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Systematic Review of Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin

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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

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Prepared by:
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Investigators:
To be added for final version

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Highway Traffic Safety Administration (NHTSA) requested and provided funding for this report.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer (TOO) named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Sharon Arnold, Ph.D.
Acting Director
Agency for Healthcare Research and Quality

Arlene Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Lionel Bañez, M.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

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Key Informants

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report will be added for the final version.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows who participated in reviewing the report will be added for the final version.

Systematic Review of Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin

Structured Abstract

Introduction. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the among the most common malignancies in the U.S. There are many potential management strategies for BCCs and SCCs, and the choice of management strategy for an individual patient is not straightforward. We aimed to comprehensively collect information on the comparative effectiveness and safety of each of currently used therapeutic strategies for both BCC and SCC.

Data sources. We conducted literature searches in MEDLINE®, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, and Embase® up to June 2016. We also perused the reference lists of published relevant clinical practice guidelines and systematic reviews. We recorded information on recurrence, histologic clearance, clinical clearance, patient or observer-rated cosmetic outcomes, adverse effects, quality of life, costs and resources, mental health, patient satisfaction, and mortality. We estimated intervention effects (differences in outcomes between treatments) and the mean frequency of the outcome with each treatment using network meta-analyses. The PROSPERO protocol registration number is CRD42016043353.

Results We systematically identified 57 randomized controlled trials and 45 non-randomized comparative studies comparing 21 interventions in 9 categories. Nearly all reported results for recurrence or cure rate outcomes and adverse events, and many reported results for cosmetic outcomes. Few studies reported results using validated instruments for quality of life, mental health, or patient satisfaction with treatment. Data were sparse, especially for individual-intervention-level analyses. Recurrence rates, for which the most data were available, are presented here. Please refer to the full report for other outcomes. For BCCs, surgical interventions and radiation were associated with lower recurrence rates than interventions that destroy lesions with heat or cold and photodynamic therapy (PDT), and may have lower recurrence rates than curettage. The data were not sufficient to draw conclusions about the comparison of curettage with interventions that destroy lesions with heat or cold or PDT, and the relative effects of interferon versus other intervention categories. For SCC in situ, interventions that destroy the lesions with heat or cold and PDT were associated with lower recurrence rates than 5-flouoruracil. Data on the relative effect of thermal interventions versus PDT were not precise enough to draw conclusions.

Conclusions. Based on sparse evidence, surgical, radiation and topical drug treatments have lower recurrence rates than other modalities for the treatment of low-risk BCC, and PDT appears to have superior cosmetic outcomes. Large gaps remain in the literature regarding the comparison of individual interventions, and very little or no information on immunocompromised patients, patients with limited life expectancy, and on patients with specific lesion categories, including high risk BCCs and invasive SCCs. More research is needed.

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Executive Summary

Introduction

Skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies in the U.S.[1] BCC and SCC, the 2 most common skin cancers, are collectively referred to as keratinocyte carcinomas. Over 5.4 million of these lesions are diagnosed in 3.3 million people in the U.S. annually.[2, 3] Generally keratinocyte carcinomas are not aggressive and do not metastasize or kill as often as melanoma, which is the third most common skin cancer.[4] However, SCC can metastasize and is estimated to kill between 3900 and 8800 people in the U.S. each year.[5] A more common problem is that basal and squamous cell carcinomas and their treatment may result in disfigurement or disability, which can adversely impact quality of life.[3] The recent Surgeon General's call to action to prevent skin cancer at the population level emphasizes the public health importance of dealing with these cancers.[6]

There are many potential management strategies for BCC and SCC, including surgical excision without intraoperative evaluation of the margins, surgical excision with intraoperative evaluation of the margins, destruction via temperature gradients, ionizing radiation, photodynamic interventions, medical therapies, various combinations of the aforementioned therapies, and watchful waiting.

The choice of management strategy for an individual patient with a specific keratinocyte carcinoma is complex. Important factors to consider include patient factors (e.g. age, frailty, immunosuppression, and personal preference) and tumor factors (e.g. histologic subtype, size, and location). There is general agreement that surgical removal is the gold standard. However, despite several dozen randomized controlled trials (RCTs) and nonrandomized comparative studies it is not clear how various surgical techniques and other therapeutic options perform relative to each other, and none of the existing reviews on this topic to date includes all treatment modalities for both BCC and SCC. The lack of clarity regarding the comparative efficacy and safety of the available options overall and in specific circumstances further complicates the choice of treatment for both physicians and patients. In addition, interventions for treating skin cancers differ substantially in cost and, given how common they are, have a huge economic impact.[3, 7-9] Payers are faced with increased utilization of costly therapies, such as brachytherapy, without clear evidence for relative benefits to justify increased costs.[10]

The objective of this systematic review is to comprehensively synthesize information on the comparative effectiveness and safety of each of the above-mentioned therapeutic strategies for both BCC and SCC.

The Key Questions

The review addresses two key questions for adult patients with basal cell or squamous cell carcinoma of the skin. Each key question will be answered separately for SCC and BCC:

Key Question 1: What is the comparative effectiveness of various interventions, overall and in subgroups of interest?

Key Question 2: How do the adverse events associated with the various interventions compare overall and in subgroups of interest?

Methods

The Brown Evidence-based Practice Center (EPC) conducted this review based on a systematic review of the published scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[11] The Prospero registration number is CRD42016043353.

Eligibility Criteria

We use the Population, Intervention, Comparator, Outcomes, and Designs (PICOD) formalism to define the characteristics of the eligible studies for this review.

Population

For both key questions, the population of interest is people with primary squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). We were interested in the following sub-populations: (1) people who are immunocompromised, including those who have had a solid organ or bone marrow transplant, human immunodeficiency virus (HIV), chemotherapy, Chronic Lymphocytic Leukemia (CLL) or other leukemias and lymphomas, or other iatrogenic; (2) people with a limited life expectancy (e.g., the very elderly, those with terminal cancer, those with end stage renal disease). We excluded sub-populations based on rare genetic factors (e.g., basal-cell nevus syndrome and xeroderma pigmentosa).

In addition, we were interested in subgroups as defined by location (e.g. face, hands, trunk, or extremities) and grade of lesion (e.g. superficial or nodular BCC or SCC in situ [Bowen's disease] in SCC).

Intervention

The interventions of interest are organized into intervention categories (A through J):

A.	Surgical excision without intraoperative evaluation of the margins
B.	Surgical excision with intraoperative evaluation of the margins Mohs micrographically controlled surgery Surgery with examination of frozen sections
C.	Interventions that destroy the lesion via temperature gradients (C1) Cryotherapy (C2) Diathermy/electrodesiccation (C3) Curettage of the lesion plus diathermy (cauterization) of margins (C4) Curettage of the lesion plus cryotherapy (C5) CO_2 laser therapy
D.	Interventions that destroy the lesion with ionizing radiation (D1) External beam radiation with photons (X or gamma rays), electrons (beta rays), or positively charged particles (e.g., protons, helium nuclei/alpha rays), at orthovoltage or megavoltage energies, or using in-office radiation machines (eg. SENSUS machines (gamma rays only) (D2) Brachytherapy with superficial application or interstitial application (pleisiotherapy) of radiation sources (usually emitting beta or alpha rays)
E.	Photodynamic interventions

	(E1) 5-aminolevulinic acid (ALA) + blue light (E2) Methyl aminolevulinate (MAL) + red light (E3) Other forms of PDT
F.	Medical interventions (F1) 5-fluorouracil (5-FU) (F2) Imiquimod (F3) Interferon (IFN alpha-2a/2b or INF beta) (F4) Ingenol mebutate (F5) Other medical interventions, including BEC-5 cream, Bleomycin, Methotrexate, Diclofenac, and Hedgehog inhibitors (Vismodegib, Sonidegib)
G.	Shave excision
H.	Curettage without diathermy
I.	Placebo
J.	No treatment

Outcomes

We evaluated the following outcomes: recurrence, histological clearance, clinical clearance, cosmetic outcomes, quality of life (as measured by validated generic and disease specific instruments), mental health (including anxiety, depression, intrusive thoughts), patient satisfaction with treatment (measured with validated disease specific instruments), mortality, and adverse events (leading to treatment discontinuation, defined as "serious", pain after treatment, and infection of the treated site).

Design

We evaluated all randomized controlled trials (RCTs) and all comparative non-randomized controlled studies (NRCSs) that took steps to control for patient- or lesion-level confounders such as medical history, age, education, lesion type, size, location and stage. NRCSs that report only crude results were identified and tabulated but were excluded from the analysis.

We also excluded studies enrolling fewer than 10 people total because they were unlikely to yield precise or broadly applicable conclusions. We excluded non-English studies, as there were very few of them and there is empirical evidence that excluding them typically has minimal impact on conclusions, especially for mainstream clinical topics.[12] Studies in any setting were acceptable.

Evidence Identification

We conducted literature searches of studies in PubMed, the Cochrane Central Trials Registry, the Cochrane Database of Systematic Reviews, and EMBASE in June 2016 to identify primary research studies meeting our criteria. All citations found by literature searches and other sources were independently screened by two researchers.

Data Extraction and Data Management:

Each study has been extracted by one member of the review team, which includes clinicians and methodologists. The extraction was reviewed and confirmed by at least one other experienced methodologist. Any disagreements were resolved by discussion among the team. Data was extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov).

Assessment of Methodological Risk of Bias of Individual Studies

We assessed elements of the design of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[13] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used relevant questions from the Newcastle Ottawa Scale.[14] We obtained a minimum bound for the number of unpublished studies through a clinicaltrials.gov search.

Data Synthesis

All included studies were summarized in narrative form and in summary tables that include the important features of the study populations, design, intervention, outcomes, and results. Lesions were divided by subtype (superficial, nodular, or high-risk BCC, SCC, or mixed populations) for analysis to ensure that the treatments would be most comparable. Where possible, lesions were also evaluated by size and location. Arms with fewer than 5 lesions were not included in the analysis, because they contribute minimal information, and in some instances, necessitated adding model parameters that were difficult to estimate.

We conducted pairwise and network meta-analyses with mixed effects (random intercepts and fixed intervention slopes) or full-random effects (random intercepts and random slopes) multilevel models within the generalized linear and latent mixed models. To aid the interpretation of these analyses we also present model-based estimates for the mean frequency of an outcome in the examined interventions, as well as forecasts of the frequency of the outcome in a new setting (e.g., a new study, or in a new population) that is similar to the studies in the meta-analysis.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

For each major conclusion, we graded the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[11] We judged the applicability within and across studies with reference to demographics of enrolled participants (e.g. age and sex distributions), the location and severity of the lesions, and the availability of treatments (e.g. various radiation machines).

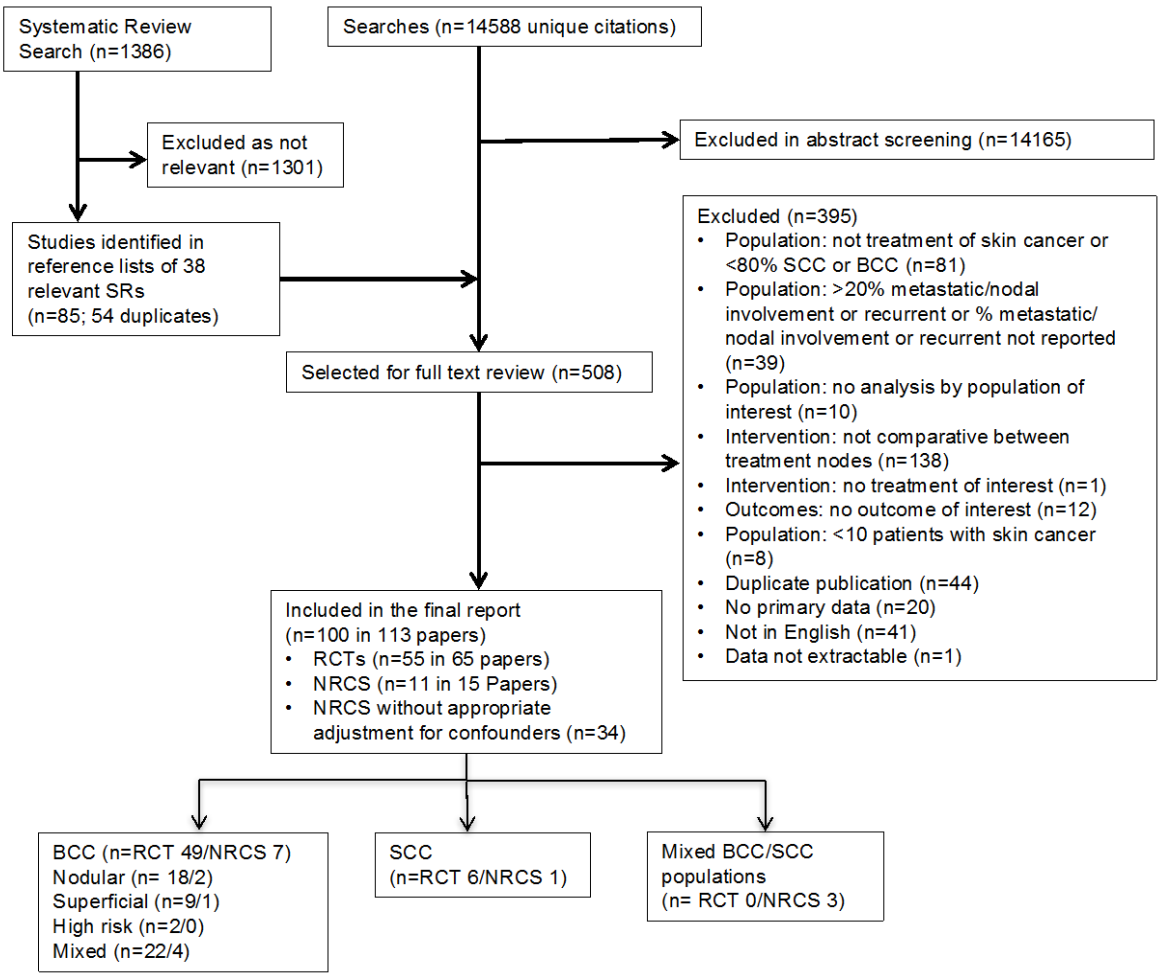
Peer Review

A draft version of this report will be reviewed by invited and public reviewers. Revisions of the draft will be made, where appropriate, based on their comments. The draft and final reports will also be reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

The literature searches yielded 14588 citations (Figure A), of which 14165 were excluded in abstract screening. A search of the reference lists of relevant systematic reviews yielded another 85 studies, which brought the total number screened in full text to 508. The 101 included studies (described in 113 papers) report 55 RCTs and 45NRCSs.

Figure A. Literature Flow Diagram



The studies primarily reported on Basal Cell Carcinoma (BCC), with a minority reporting results for Squamous Cell Carcinoma (SCC). Nearly all reported results for recurrence or cure rate outcomes and adverse events, and many reported results for cosmetic outcomes. Few studies reported results using validated instruments for quality of life, mental health, or patient satisfaction with treatment. Because there was insufficient evidence for these outcomes, these results are presented in the full report only, as are results for specific types of BCC and other subgroups.

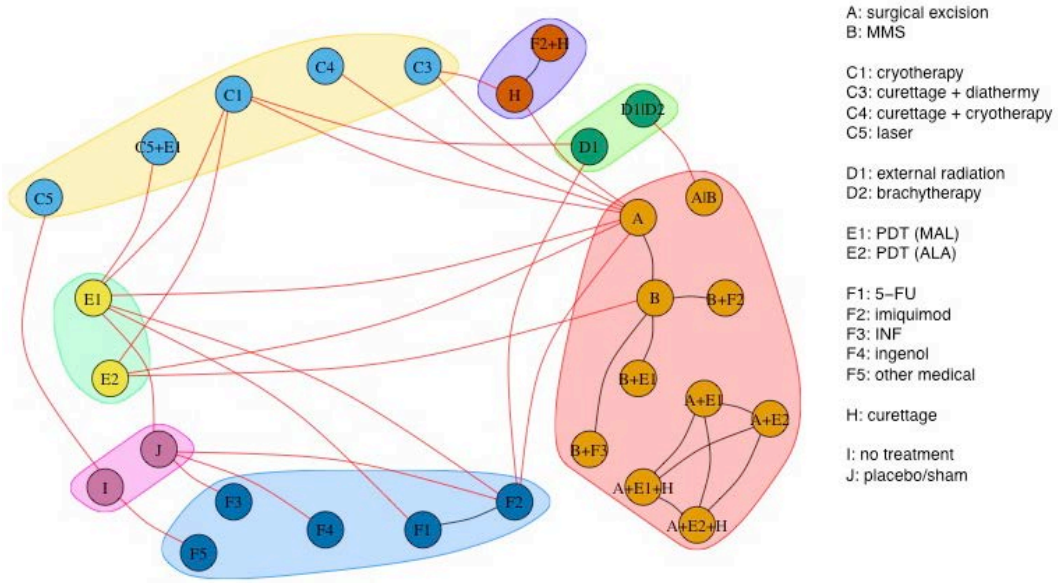
Details on how to read the graphs and tables are provided in the methods section of the full report.

Basal Cell Carcinoma (BCC)

The evidence graph in Figure B shows that there are 35 comparisons that have been studied between 28 interventions organized in 7 intervention categories. This evidence graph suggests that limited conclusions can be drawn about which individual intervention is best (with respect to each outcome) for two reasons: 1) some interventions have never been compared with other interventions, directly or indirectly, and 2) There are few studies for any given comparison.

The evidence is even more sparse when one considers the information that is actually available for specific outcomes. Figure C shows the evidence graphs for the outcomes for which we have the most data, namely recurrence, lack of histologic clearance, and lack of clinical clearance. For these outcomes, no RCT data exist for 14, 8, and 14 of the 28 interventions, respectively. Evidence on other outcomes (quality of life, cosmetic outcomes, and costs or resource use) is even more sparse, as discussed in the following sections. The evidence remains sparse at the level of individual interventions even after considering results from the seven eligible NRCSs, which are not mentioned in this executive summary but are summarized in the full report.

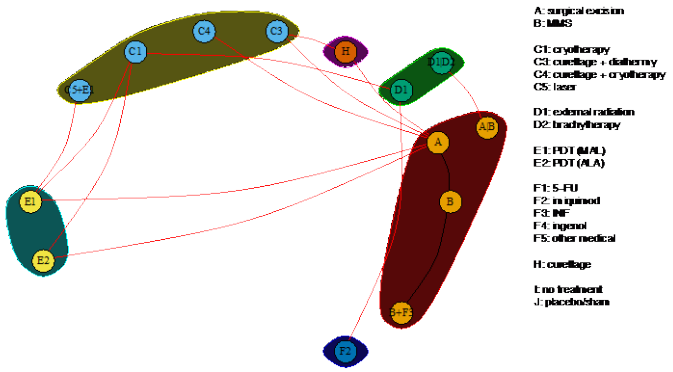
Figure B: Evidence graph depicting compared treatments in RCTs of BCC lesions.



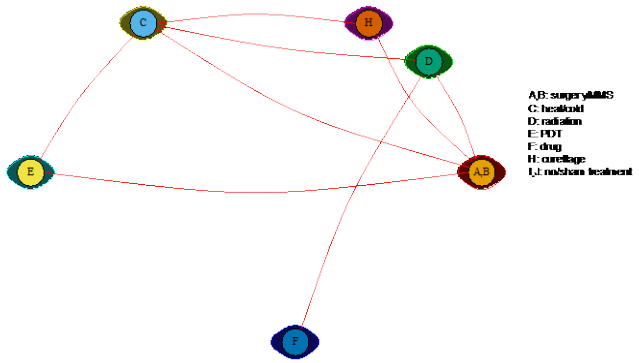
The RCTs included patients and lesions that are typically encountered in clinical practice, but the lack of information on treatment effect heterogeneity with respect to patient-level factors limits extrapolation to individual patients. No RCT focused on patients who were immunocompromised or had substantially limited life expectancy.

Figure C: Evidence graphs for recurrence, histologic clearance and clinical clearance from RCTs of BCC lesions

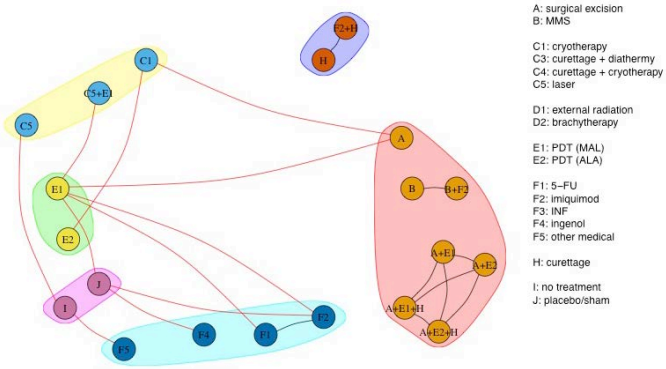
(A) Recurrence (interventions)



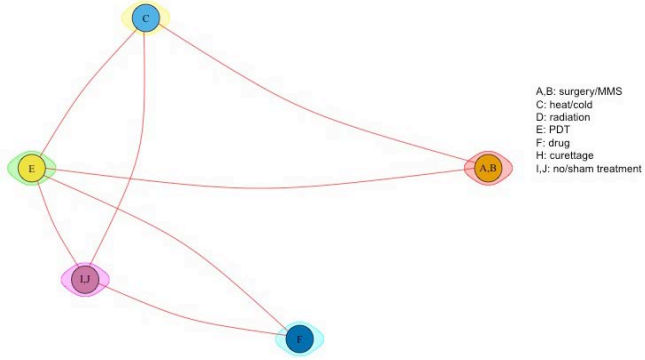
(Intervention types)



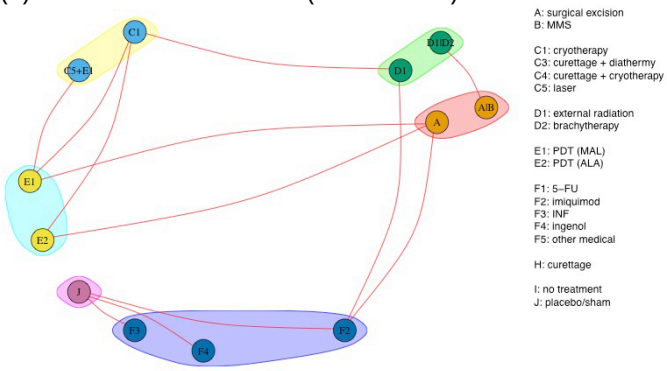
(B) Lack of histologic clearance (Interventions)



(Intervention types)



(C) Lack of clinical clearance (interventions)



(Intervention types)

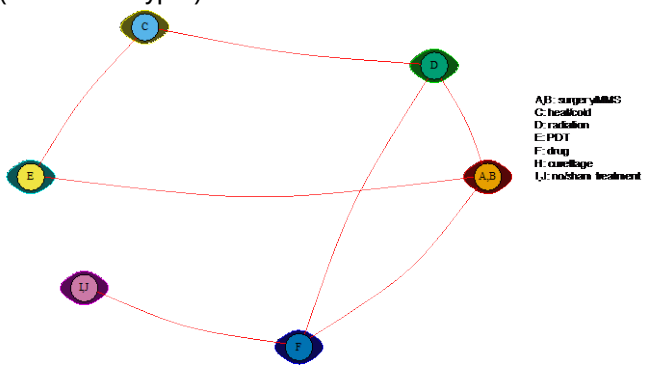


Table A. Mean frequency (percent) of outcomes per intervention category based on direct and indirect data (all BCCs)

Intervention type	Recurrence	Lack of histological clearance	Lack of clinical clearance	Cosmetic outcomes: patient reported	Cosmetic outcomes: observer reported	AEs leading to discontinuation	Serious AEs	AEs: pain	AEs: infection
surgery/ MMS (A,B)	3.4 (1.5, 7.6)	1.2 (0.1, 15.9)	2.9 (0.7, 10.7)	88.8 (73.7, 95.7)	55.0 (34.7, 73.8)	Not defined**	0.6 (0.2, 2.4)	21.5 (8.1, 46.2)	5.5 (2.8, 10.7)
Heat/cold (C)	21.4 (13.8, 31.6)	24.9 (8.2, 55.0)	9.7 (2.9, 27.9)	60.5 (32.4, 83.0)	74.3 (51.5, 88.8)	0.9 (0.0, 20.1)	2.6 (0.2, 31.0)	12.9 (0.8, 73.1)	NA
Radiation (D)	4.4 (1.8, 10.4)		4.5 (0.7, 23.6)	79.1 (55.2, 92.1)	25.5 (7.1, 60.7)				
PDT (E)	23.0 (14.8, 33.9)	19.5 (6.4, 46.4)	14.2 (5.4, 32.6)	97.9 (93.1, 99.4)	88.7 (78.9, 94.2)	Not defined**	0.7 (0.2, 2.7)	20.7 (8.2, 43.3)	0.5 (0.1, 2.4)
Drugs (F)	3.1 (0.2, 38.8)	35.6 (16.5, 60.8)	16.4 (5.0, 42.3)	94.2 (37.5, 99.8)	76.3 (52.8, 90.2)	4.9 (2.0, 11.6)	3.6 (2.0, 6.5)	9.9 (4.4, 20.9)	0.5 (0.1, 3.7)
Curettage (H)	20.0 (5.5, 51.9)								
No/sham treatment (I,J)		83.5 (65.5, 93.1)	84.2 (50.6, 96.5)		89.8 (40.1, 99.1)	1.0 (0.2, 4.4)	2.4 (0.3, 15.2)	2.9 (0.9, 9.4)	NA

** Surgical interventions and PDT are one-time therapies that cannot be "discontinued". For parsimony of exposition, however, in the descriptive analyses in the Table we assigned 0 discontinuation to these interventions. AE= adverse event; MMS=Mohs micrographic surgery; PDT=photodynamic therapy

Recurrence

In total, 11 RCTs (1234 lesions) were included in this analysis, and cumulative sample sizes per comparison ranged from 27 to 347.

For parsimony of exposition, we only list predicted mean frequencies of events with each intervention category across the included RCTs, based on their estimated relative effects in network meta-analysis (Table A). (For more results, refer to the full report.) That is, we combined raw frequency data from RCTs for each intervention with their relative effects to calculate an estimated frequency for each event.

Surgical treatments, radiation, and drug treatments had average recurrence in the 3.1 to 4.4 percent range compared to photodynamic therapy, curettage, and interventions that destroy lesions with heat or cold, which had much higher average recurrence rates, in the 20 to 23 percent range. The average recurrence rates for individual interventions follow the same pattern as the corresponding recurrence rates for intervention categories. For example, the mean recurrence rate for surgical excision (A), MMS (B), and a combination of MMS and interferon (B+F3) ranged between 4.0 and 4.6 percent; and it was estimated at 3.4 percent for surgical interventions (A,B).

Lack of histological clearance

In total, 15 RCTs (1940 lesions) were included in this analysis, and cumulative sample sizes per comparison ranged from 27 to 380. Table A shows the mean fraction of lesions without histologic clearance across the included RCTs. (For more results, refer to the full report.) The average number of lesions with no histological clearance was 1.2 percent in surgical treatment

arms, between 19.5 and 35.6 percent in other active intervention categories, and 83.5 percent for no or sham (placebo) treatment.

Lack of clinical clearance

In total, 14 RCTs (1734 lesions) were included in this analysis, and cumulative sample sizes per comparison ranged from 27 to 380. For each intervention category, Table A shows the mean fraction of lesions without clinical clearance across the included RCTs. (For more results, refer to the full report.) The average number of lesions with no clinical clearance was 2.9 percent in surgical treatment arms, between 4.5 and 16.5 percent in other active intervention categories, and 84.2 percent for no or sham treatment. In general, the mean fractions for lack of histologic clearance for individual interventions are in congruence with the corresponding fractions estimated for intervention categories.

Patient-reported cosmetic outcomes, all BCC lesions

In total, seven RCTs (752 lesions) were included in this analysis. In Table A drugs (F; 94.2%) and PDT (E; 97.9%) are associated with highest percentages of good cosmetic outcomes, followed by surgical treatments (A,B; 88.8%), radiation (D; 79.1%), interventions that use heat or cold to destroy the lesion (C; 60.5%). (For detailed results, refer to the full report.)

Observer-reported cosmetic outcomes, all BCC lesions

In total, 10 RCTs (1460 lesions) were included in this analysis. In Table A the percentage of lesions with good or better cosmetic outcomes ranged between 74.3 and 89.8 percent for interventions that destroy the lesion with heat or cold (C), drugs (F), PDT (E) and no or sham treatment (I,J), and was 55.0 percent for surgical treatments (A,B). Radiation (D) had the smallest percentage of good or better cosmetic outcome. However, the confidence intervals for these proportions are wide, so we could not draw any strong conclusions.

Adverse events, all BCC lesions

In Table A drugs were most likely to have adverse events leading to discontinuation (4.9%; 95% CI, 2.0 to 20.1); other interventions types had a much smaller percentage (1.2%). (Some treatments (e.g. surgical, temperature, and some PDT) are one-time procedures, with no option for discontinuation.) The number of adverse events characterized as “serious” by the investigators was smaller than 3.6 percent for all intervention categories. Pain after treatment was most commonly encountered for surgical interventions (21.5%) and for PDT (20.7%), and was least common with sham treatments (2.9%). Infections at the treatment site were described in 5.5 percent of lesions with surgical treatments (95% CI 28 to 10.7), and were reported in less than 1 percent for PDT and drugs. No information on infections was available for treatments that destroy lesions with heat or cold or for no (or sham) treatment.

Squamous Cell Carcinoma (SCC)

The evidence graph in Figures D and E depict eight comparisons between 10 interventions organized in four intervention categories, none of which are in the surgical or radiation category. All RCTS included only participants with SCC in situ (SCCIS). Comparisons between individual interventions are sparse, suggesting that limited, if any, conclusions can be drawn about which individual treatment is best for each outcome. Figure D has two connected subgraphs. The smallest one compares a laser-based preparation of the lesion for PDT treatment (C5+E2) versus

PDT alone (E2), and the other comprises all other treatments. Information on each comparison is provided by at most three RCTs, and for most comparisons, by a single RCT.

Figure E shows the corresponding evidence graphs for the outcomes for which we have the most data, namely recurrence, lack of histologic clearance, and lack of clinical clearance. RCT data exists for only 7, 4, and 8 of the 28 interventions, respectively. Evidence on other outcomes (quality of life, cosmetic outcomes, costs or resource use) is even sparser.

Figure D: Evidence graph depicting compared interventions in RCTs of SCC lesions

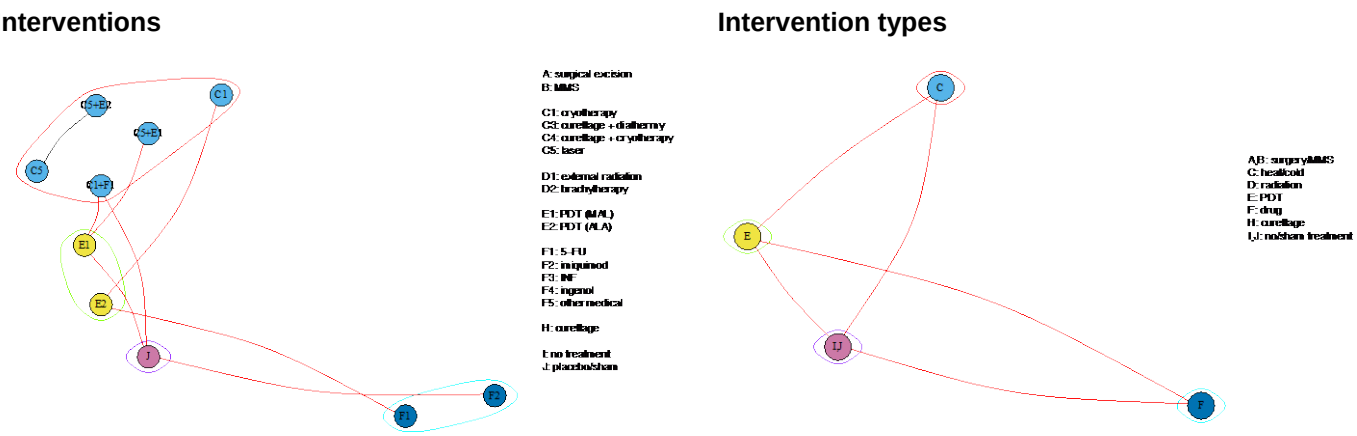
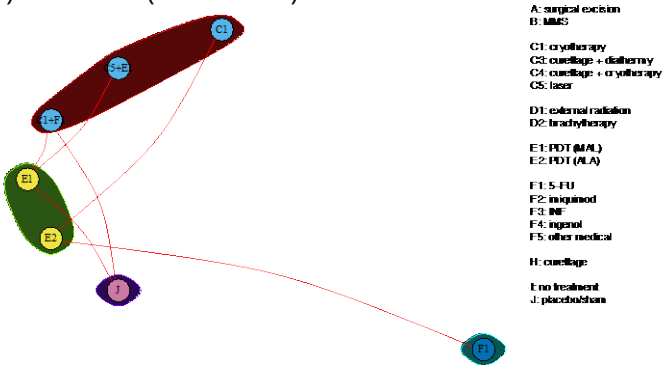
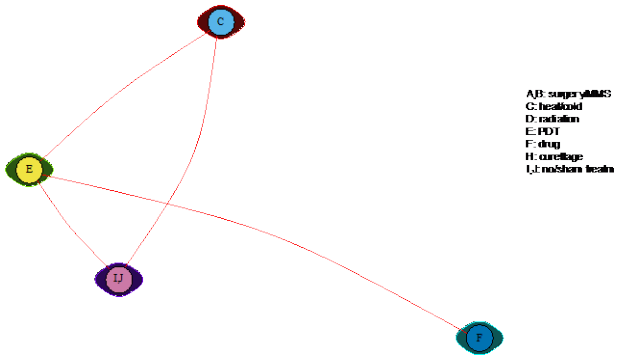


Figure E: Evidence graphs for recurrence, histologic clearance, and clinical clearance for RCTs of SCC lesions

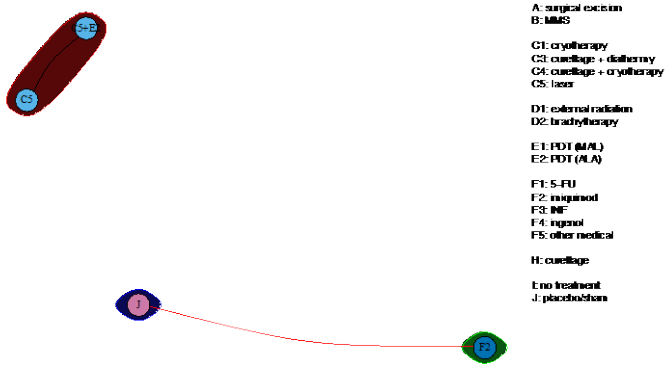
(A) Recurrence (Interventions)



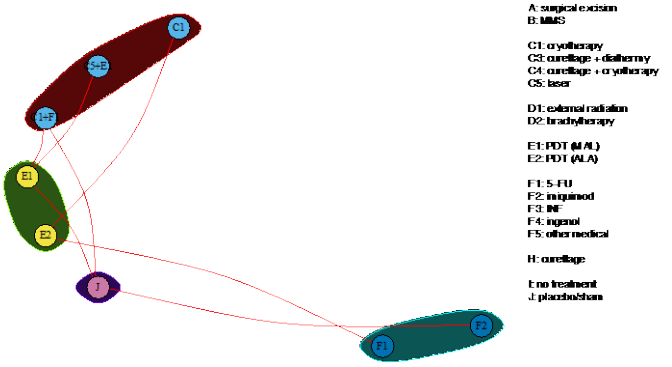
(Intervention types)



(B) Lack of histologic clearance (Interventions)



(C) Lack of clinical clearance (Interventions)



(Intervention types)

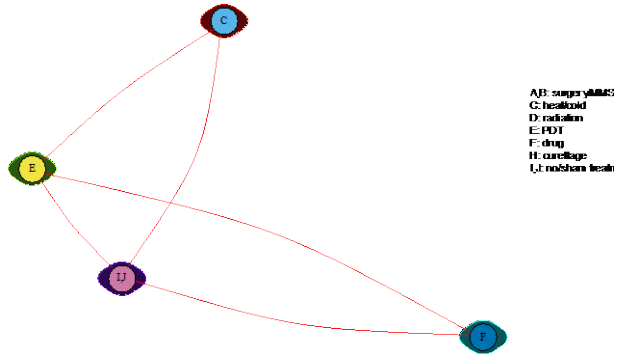


Table B Mean frequency of outcomes per intervention category based on direct and indirect data (SCCIS)

Treatment type	Recurrence rates	Lack of clinical clearance	Adverse events leading to discontinuation	Serious Adverse events	Adverse events: pain after treatment	Adverse events: infection
heat/ cold (C)	15.1 (8.1, 26.5)	10.8 (3.1, 31.3)	1.9 (0.6, 6.4)	0.9 (0.1, 6.1)	34.1 (20.0, 51.6)	0 (0, 31)
PDT (E)	17.7 (10.8, 27.8)	14.9 (5.4, 34.9)	Not defined**	0.5 (0.0, 7.7)	23.4 (12.4, 39.5)	0 (0, 31)
Drugs (F)	51.5 (28.9, 73.5)	29.2 (8.4, 65.1)	13.3 (3.4, 40.5)	NA	NA	NA
No/ sham treatment (I,J)	50.0 (11.2, 88.8)	88.0 (54.2, 97.8)	4.7 (0.9, 20.1)	0 (0, 32.2)	28.4 (9.7, 59.3)	NA

** PDT is a one time interventions that cannot be "discontinued"; for parsimony of exposition, however, in the descriptive analyses in the Table we assigned 0 discontinuation events to PDT. AE= adverse event; PDT=photodynamic therapy.

Recurrence

In Table B interventions that destroy the lesion with heat or cold (C) and PDT (E) had on average lower recurrence rates (15.1 and 17.7 percent, respectively) compared to drugs or no/sham treatment. Of note, the average recurrence rate with drugs is 51.5 percent (95% CI 28.9 to 73.5), reflecting the high recurrence rates observed in the single RCT comparing 5-FU with PDT (ALA) in this analysis.

Lack of histological clearance

Data were very sparse (2 RCTs, 50 lesions), and results are not summarized here. Refer to the full report.

Lack of clinical clearance

In Table B the fraction of lesions without clinical clearance was between 10.8 and 29.2 percent in the active treatments and 88 percent with placebo, which is similar to the results by individual comparisons. However, the confidence intervals for each estimate are wide.

Patient-reported cosmetic outcomes, all SCC lesions

We did not identify any studies with results for this outcome in this population.

Observer-reported cosmetic outcomes, all SCC lesions

Data were very sparse (2 RCTs, 204 lesions), and results are not summarized here. Refer to the full report.

Adverse events, all SCCIS lesions

In Table B the highest mean frequency of adverse events leading to treatment discontinuation (3 RCTs; n=292) was 13.3 percent (95% CI, 3.4 to 40.5) for drugs (F); it was less than 1.2 percent for other intervention categories. The frequency of adverse events characterized as "serious" by the investigators (1 RCT; n=225) was smaller than 1 percent for all intervention categories. In the two RCTs that reported pain after treatment, between 23.4 and 34.1 percent reported pain regardless of treatment (including sham treatments). The outcome of infection at the treatment site was reported in a single RCT (n=36) at 0 percent.

Discussion

Within the existing evidence, with respect to BCC recurrence, surgical treatments and radiation therapy appear to be (statistically significantly) better than interventions that destroy lesions with heat or cold, PDT, or curettage. However, PDT was associated with improved cosmetic outcomes. With regards to drugs for the treatment of BCC, interferon was the only drug for which a randomized comparison for recurrence was identified. While it was associated with low recurrence rates, the confidence intervals were wide and so we cannot rule out excellent or poor results for that intervention category.

Given that lack of recurrence is, essentially, cure from disease, these results support the use of surgical and radiation treatment for low-risk BCC. For SCCIS, the use of cryotherapy and PDT is supported over topical 5-fluorouracil with regards to recurrence. However, how these treatments perform for SCCIS compared with surgical treatments, which are commonly used in clinical practice, is not ascertainable based on the currently available evidence.

For patients and clinicians, though, cure is not the only important endpoint. Surgery, radiation and each of the other treatments under study are associated with benefits and drawbacks that patients and clinicians consider routinely. For example, while external beam radiation therapy is effective, its remote sequelae, such as skin atrophy and the development of secondary tumors, make it less advisable for younger patients. For patients for whom cosmesis is a primary concern, treatment with PDT may be preferable despite its higher recurrence rates. Despite sparse evidence on their ability to cure BCC and SCCIS, some patients may prefer the convenience provided by topical medical treatments such as 5-fluorouracil and imiquimod which can be applied by the patient at home; this contrasts with the multiple visits to hospitals or specialty clinics required for radiation therapy which are not be practical for some patients. Access to treatments will also impact clinical decisionmaking; specialty care is not available in all communities; while primary care physicians can perform basic surgical procedures and prescribe topical medications, they do not have access to specialized treatments such as MMS, radiotherapy and PDT.

Perhaps the most striking observation is the dearth of information that is available comparing interventions for these very common cancers. For example, only 11 RCTs (n=1234 lesions) examining BCC recurrence were included, of which only 15 lesions were treated with a drug (interferon) and only 20 were treated with curettage. Further, the amount of evidence in the 8 comparisons with head to head data was limited: the number of RCTs per comparison ranged between 1 and 3, and the cumulative number of lesions ranged between 27 and 347.

For SCC, data on recurrence are even sparser. For SCCIS, only 4 RCTs (348 lesions) compared 4 types of interventions, namely a drug (imiquimod), interventions that destroy lesions with heat or cold, PDT, and sham treatments (Figure 16 [B] and Table 46). Note that surgical interventions and curettage, therapies commonly used for SCCIS in clinical practice, were not examined.

No RCT evaluated treatments for invasive SCC, the subgroup of SCC that are most likely to recur or metastasize, and thus most important to evaluate. In clinical practice, these lesions are routinely treated with surgical excision with or without intraoperative margin evaluation, and in most cases are considered appropriate for Mohs surgery in the American Academy of Dermatology appropriate use criteria.[19] Radiation is also commonly used for invasive SCC. The lack of evidence comparing efficacy among these commonly used treatments is striking.

With few exceptions and for most outcomes, individual studies were deemed to have at most moderate risk of confounding, selection, or measurement biases. The risk of bias of individual

studies was not a major determinant for the conclusions in the Tables. By far the major concern is that the evidence is sparse when one considers the richness of the clinical questions that can be posed. Comparisons between intervention categories are not as informative as comparisons between individual interventions. We have provided analyses at the individual intervention level, but opt not to draw conclusions based on them, because most are based on indirect data and small numbers.

Another consequence of the paucity of evidence base is that one cannot directly address questions that may have important health and cost implications for insurers and patients. For example, there are no studies on the effectiveness of external radiation therapy delivered with portable machines in the office setting versus radiation therapy delivered in specialized facilities or versus other interventions. Empirical data on this radiation therapy modality would be useful because there are only limited data on radiation therapy to extrapolate from.

Other large gaps remain in the knowledge base: There is no information on subgroups of patients who have limited life expectancy, are frail, or who are immunocompromised (e.g., have CLL and other malignancies, immunodeficiency disorders, or who receive immunomodulating or immunosuppressive treatments). There is limited or no information on high risk BCC lesions, and on invasive SCCs. There is limited data on patient- and lesion-specific modifiers of intervention effects.

Finally, outcomes such as histological clearance and clinical clearance are surrogates for lesion recurrence. In particular, clinical clearance may help physicians choose among PDT, medical, and radiation-based therapies, but is not an informative outcome for surgical interventions: any surgical treatment, regardless of margin control, removes all clinically visible tumor. Therefore, our conclusion in Table 61 that surgical interventions are better than all other interventions with respect to clinical clearance, while very likely to be true, is almost meaningless.

Evidence Gaps

We have identified a number of important gaps in the medical literature on the topic of treating BCC and SCC. First, more trials are needed comparing commonly used treatment modalities such as simple excision, Mohs surgery, PDT and topical medical therapy. Further, in order to justify routine use of various forms of radiotherapy for these patients, more trials comparing radiotherapy with other modalities are needed. As it stands, the lack of evidence on radiotherapy has led the American Academy of Dermatology to discourage the use of superficial radiotherapy and electronic brachytherapy for keratinocyte carcinomas except in select patients.[15, 16] As these tumors are very common and generally have low morbidity and mortality, recruitment for such trials may not prove to be prohibitively difficult.

Second, all trials for BCC and SCC should, where possible, use recurrent disease as a primary or secondary outcome as it is the most clinically important outcome. Trials should also attempt to incorporate measures of healthcare resource utilization, which were lacking in our review of the existing evidence save for one RCT and one NRCS.[17, 18]

Third, while more evidence is needed overall, future research should also focus on specific subgroups that have minimal evidence to date. Aggressive histologic subtypes of BCC, including infiltrative and sclerosing patterns, account for very little of the evidence found in our review. While their increased likelihood of recurrence has led to their inclusion as appropriate indications for Mohs surgery (except for lesions ≤0.5 cm on the trunk and extremities, whose appropriateness is rated as “uncertain”), there is scant evidence to support this.[19] With regards to

SCC, the only RCT evidence included in this report concerns in situ disease. Given that invasive SCC is responsible for mortality in 3900-8800 people in the U.S. each year[5] in addition to morbidity and healthcare, there is a clear need for comparative effectiveness research for invasive SCC treatments. No comparative evidence was found on keratinocyte carcinomas in high-risk groups such as organ transplant recipients and patients with other altered immune states such as HIV and Chronic Lymphocytic Leukemia (CLL). Patients with limited life-expectancy are another subgroup of interest who warrant study.

Fourth, better monitoring of population trends in BCCs and SCCs can help focus research on the most consequential subtypes. Such monitoring can be performed by SEER (which currently ignores these cancers), the CDC, or large health organizations taking advantage of advances in health information technology.

Patients, clinicians, payers, and research funders would benefit from a decision analysis of the management of BCC and SCC lesions.

Conclusions

Based on sparse evidence, surgical, radiation and topical drug treatments have lower recurrence rates than other modalities for the treatment of low-risk BCC, and PDT appears to have superior cosmetic outcomes. Large gaps remain in the literature regarding the comparison of individual interventions, and very little or no information on immunocompromised patients, patients with limited life expectancy, and on patients with specific lesion categories, including high risk BCCs and invasive SCCs. In order for clinicians, patients and payers to make informed decisions regarding the treatment of these lesions, new RCT or high-quality NRCS evidence is needed.

Table C. Summary conclusions for BCC lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, all BCC						
(1) Surgical interventions (A,B) and radiation (D) were associated with lower recurrence rates than interventions that destroy lesions with heat or cold (C), and PDT (E) (moderate to high strength of evidence) (2) Curettage (H) may have higher recurrence rates than surgical interventions (A,B) or radiation (D) (3) [Imprecise data on the comparison on curettage and interventions that destroy lesions with heat or cold (C) or PDT (E)] (4) [Imprecise data on the relative effects of interferon (F) versus other intervention categories]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 7 and 8)	Mix of direct and indirect data	(1) Moderate to High (2) Low (3) [Insufficient] (4) [Insufficient]	• Surgery/MMS (A,B) had significantly fewer recurrences than heat/cold, PDT, and curettage; not significantly fewer than radiation; and not significantly more than drugs (7 RCTs; 2 NRCSs) • Heat/cold (C) interventions had significantly more recurrences than surgery and radiation; not significantly more than drugs and curettage, and not significantly fewer than PDT (7 RCTs) • Radiation (D) had significantly fewer recurrences than thermal interventions and PDT, not significantly fewer than curettage, and not significantly more than surgery and drugs (3 RCTs) • PDT (E) had significantly more recurrences than radiation and surgery, and not significantly more than heat/cold, drugs, and curettage (6 RCTs, 1 NRCS) • Interferon (F) had fewer recurrences than all other interventions, but not significantly in any case (1 RCT, 1 NRCS) • Curettage (H) had significantly more recurrences than surgery, not significantly more recurrences than drugs and radiation, and not significantly fewer recurrences than PDT and heat/cold (2 RCTs)
Histologic clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better histological clearance outcomes and were statistically significantly better than interventions that destroy lesions with heat or cold (C), PDT (E), drugs (F), and placebo (I,J). (2) Interventions that destroy lesions with heat or cold (C), PDT (E), and drugs (F) have better histological outcomes than placebo (I,J) (3) [imprecise data on the relative comparisons of non-surgical active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 17 and 18)	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed significantly better than heat/cold, drugs, and placebo, and non-significantly better than PDT (2 RCTs) • Thermal interventions (C) performed significantly better than placebo, non-significantly better than drugs, non-significantly worse than PDT, and significantly worse than surgery (2 RCTs) • PDT (E) performed significantly better than placebo, non-significantly better than drugs and heat/cold, and non-significantly worse than surgery (7 RCTs, 1 NRCS) • Drugs (F) performed significantly better than placebo, non-significantly worse than PDT and heat/cold, and significantly worse than surgery (8 RCTs, 2 (NRCSs)
Clinical clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better clinical clearance outcomes than PDT (E), drugs (F) and placebo (I,J) (2) All active treatments were associated with better clinical clearance outcomes than placebo (3) [Imprecise data on relative comparisons between non-surgical active treatments]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 28 and 29)	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed statistically significantly better than drugs and placebo, and non-significantly better than heat/cold and PDT (4 RCTs); this comparison is less relevant as surgery ought to achieve 100% clinical clearance • Thermal interventions (C)performed statistically significantly better than plecebo, non-significantly better than drugs and PDT, and non-significantly worse than surgery (3 RCTs) • PDT (E) performed statistically significantly better than placebo, non-significantly better than drugs, and non-significantly worse than surgery and heat/cold (7 RCTs) • Drugs (F) performed statistically significantly better than placebo, non-significantly worse than PDT and heat/cold, and significantly worse than surgery

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
						(5 RCTs)
Patient-reported cosmetic outcomes, all BCC						
(1) PDT is associated with better cosmetic outcomes than other intervention categories (2) [Imprecise data on relative comparisons between non-surgical active intervention categories]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons (Refer to Tables 38, 39)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Low (2) Insufficient	• (A,B) Surgery had significantly better outcomes than heat/cold and radiation, significantly worse outcomes than PDT, and non-significantly worse outcomes than drugs (4 RCTs) • Thermal interventions (C)had significantly worse outcomes than surgery and PDT and non-significantly worse than radiation and drugs (2 RCTs) • Radiation (D) had non-significantly better outcomes than heat/cold, non-significantly worse outcomes than drugs, and significantly worse outcomes than PDT and surgery (2 RCTs) • PDT (E) had significantly better outcomes than surgery, heat/cold, and radiation and non-significantly better outcomes than drugs (4 RCTs) • Drugs (F) had better outcomes than surgery, heat/cold, and radiation, and non-significantly worse outcomes than PDT, but not statistically significantly so (1 RCT)
Observer-reported cosmetic outcomes, all BCC						
(1) PDT is associated with significantly better cosmetic outcomes than surgery (A,B) (2) [PDT may be associated with better cosmetic outcomes compared to nonsurgical active intervention categories] (3) [Imprecise data on relative comparisons between heat/cold (C), radiation, and drugs (D)]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons (Refer to Tables 40, 41)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) [Insufficient] (3) [Insufficient]	• (A,B) Surgery had non-significantly better outcomes than radiation, significantly worse outcomes than PDT, and non-significantly worse outcomes than drugs, heat/cold, and placebo (4 RCTs, 1 NRCS) • (C) Heat/cold interventions had significantly better outcomes than radiation, non-significantly better outcomes than surgery, and non-significantly worse outcomes than PDT, drugs, and placebo (1 RCT) • Radiation (D) had significantly worse outcomes than heat/cold, PDT, drugs, and placebo, and non-significantly worse outcomes than surgery (1 RCT, 2 NRCS) • PDT (E) had significantly better outcomes than surgery and radiation, non-significantly better outcomes than drugs and heat/cold, and non-significantly worse outcomes than placebo (7 RCTs, 1 NRCS) • Drugs (F) had significantly better outcomes than radiation, non-significantly better outcomes than surgery and heat/cold, and non-significantly worse outcomes than PDT and placebo (1 RCT)
Adverse effects, all BCC						
(1) Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with surgical interventions (A,B), heat or cold (C), PDT (E) and drugs (F) (2) For the interventions above, on average, 1 in 10 to 1 in 5 patients report experiencing pain after treatment	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events have wide 95% CIs (Table 43)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) Low	• For active interventions, the percentage of discontinuation of treatment, serious adverse events, and infection of the treatment site ranged from 0/not defined to 5.5%. Forecast CIs are wide (as high as 29%; Table 43) • For active interventions, the percentage of pain after treatment ranged between 9.9 and 21.6%. Forecast CIs are wide (as high as 88%; Table 43)

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Other outcomes, all BCC						
[Evidence on quality of life, mental health, patient satisfaction, mortality, cost and resource use is reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

Table D. Summary conclusions for SCCIS lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, SCCIS						
(1) Interventions that destroy the lesions with heat or cold (C) and PDT (E) were associated with lower recurrence rates than 5 FU (F) (2) [Imprecise data on the relative effect of thermal interventions versus PDT]	Moderate	Possibly consistent (No robust indications of inconsistency)	Moderately precise. Varies by comparison from precise to imprecise. (Refer to Tables 46 and 47)	Mix of direct and indirect data	(1) Low (2) [Insufficient]	• Thermal interventions (C)had statistically significantly fewer recurrences than drugs, and not significantly fewer than PDT or placebo (2 RCTs) • PDT (E) had statistically significantly fewer recurrences than drugs, but not statistically significantly fewer than placebo or more than heat/cold (4 RCTs) • Drugs (F) had statistically significantly more recurrences than heat/cold and PDT, and not significantly more than placebo (1 RCT)
Histologic clearance, SCCIS						
(1) [Laser (C5) + PDT with ALA (E2) results in better histologic clearance over laser alone] (2) 5-FU (F) results in better histologic clearance than placebo (I,J)	(1) Low (2) High	[Not rated]	(1) Imprecise (2) Precise	(1) Direct (2) Direct	(1) [Insufficient] (2) Low	[2 RCTs, 50 patients. See Tables 51, 52]
Clinical clearance, SCCIS						
(1) Examined types of active interventions (heat/cold [C], PDT (E), and drugs [5-FU, imiquimod; F]) were associated with better clinical outcomes than placebo (2) [Imprecise data on relative comparisons between types of active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 53 and 54)	Mix of direct and indirect data	(1) High (2) [Insufficient]	• Thermal interventions (C)performed significantly better than placebo, and non-significantly better than drugs and PDT (4 RCTs) • PDT (E) performed significantly better than placebo, non-significantly better than drugs, and non-significantly worse than heat/cold (5 RCT) • Drugs (F) (5-FU, imiquimod) performed significantly better than placebo, and non-significantly worse than PDT and heat/cold (2 RCT)
Observer-reported cosmetic outcomes, SCCIS						
(1) Cryotherapy plus 5-FU (C1+F1) is associated with better outcomes than PDT (MAL) (E1) (2) [No difference between laser pre-treatment of the lesion before PDT versus PDT alone]	Low	Unclear (Consistency cannot be rated)	(1) Precise (2) Imprecise (Refer to Tables 58, 59)	Mix of direct and indirect data	(1) Moderate (2) [Insufficient]	[2 RCTs, 204 patients. See Tables 58, 59]
Adverse effects, SSCIS						

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
(1) [Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with heat or cold (C), PDT (E) and drugs (F)] (2) [On average, 1 in 4 and 1 in 3 patients report experiencing pain after treatment with PDT (E) and heat or cold (C), respectively]	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events have wide 95% CIs (Table 60)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) [Insufficient] (2) [Insufficient]	[3 RCTs 292 patients. See Table 60]
Other outcomes, SCCIS						
[Evidence on patient reported cosmetic outcomes, quality of life, mental health, patient satisfaction, mortality, cost and resource use id reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

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Introduction

Background

Skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies in the U.S.[1] BCC and SCC, the 2 most common skin cancers, are collectively referred to as keratinocyte carcinomas. Over 5.4 million of these cancers are diagnosed in 3.3 million people in the U.S. annually.[2, 3] Generally keratinocyte carcinomas are not aggressive and do not metastasize or kill as often as melanoma, which is the third most common skin cancer.[4] However, SCC can metastasize and is estimated to kill between 3900 and 8800 people in the U.S. each year.[5] Aggressive behavior is of particular concern in people who are immunosuppressed, including organ transplant recipients whose mortality is increased after being diagnosed with SCC.[6] A more common problem is that basal and squamous cell carcinomas and their treatment may result in disfigurement or disability, which can adversely impact quality of life.[3] The recent Surgeon General's call to action to prevent skin cancer at the population level emphasizes the public health importance of dealing with keratinocyte carcinomas.[7] Because of their frequency, BCC and SCC are the fifth most expensive cancer at the population level, and, being more common in older adults, their management is of great importance to Medicare.[2, 3, 8] It is estimated that in 2012 over 2 million Medicare beneficiaries underwent intervention for BCC or SCC.[2]

There are many potential management strategies for keratinocyte carcinoma, and they can be broadly grouped into eight main categories: (1) surgical excision without intraoperative evaluation of the margins, (2) surgical excision with intraoperative evaluation of the margins, (3) destruction via temperature gradients, (4) ionizing radiation, (5) photodynamic interventions, (6) medical therapies, along with (7) combinations of these therapies, and (8) watchful waiting. Surgical management is used most commonly, followed by radiation.[9-11] In individuals over 65, surgery is used to treat 61 percent of keratinocyte carcinomas (excision 42% and Mohs micrographic surgery 19%) followed by electrodessication and curettage (39%).[12] Specific surgical techniques include simple surgical excision with pre-specified margins, surgery with intra-operative margin control (e.g. Mohs micrographic surgery or excision with examination of frozen sections), and curettage, which is usually combined with secondary destruction using electrodessication.[13] Cryotherapy with liquid nitrogen is another destructive method. Ionizing radiation modalities include traditional external beam radiation as well as brachytherapy, in which radioactive implants are placed directly in the tumor. Topical medical treatments include topical chemotherapy (such as 5-fluorouracil) and topical immunomodulatory medications (such as imiquimod). Photodynamic therapy involves application of a topical photosensitizer (such as 5-aminoleveulinic acid (ALA) and methyl-ALA) followed by exposure to specific wavelengths of light to destroy tumor cells. New targeted systemic agents, such as vismodegib, for BCC[14] are also available, but are reserved for advanced or metastatic cases and are used much less commonly than the modalities listed above. Additionally, active non-intervention (watchful waiting) has recently been advanced as a therapeutic strategy, particularly for patients with decreased life expectancy.[15, 16]

The choice of management strategy for an individual patient with a specific keratinocyte carcinoma is complex. Factors that are important include patient factors (e.g. age, frailty, immunosuppression, and personal preference) and tumor factors (e.g. histologic subtype, size, and location). A lack of clarity regarding the comparative efficacy and safety of the available

options overall and in specific circumstances further complicates the choice of treatment for both physicians and patients.

There is general agreement that surgical removal is the gold standard. However, despite several dozen randomized controlled trials (RCTs) and nonrandomized comparative studies, it is not clear how various surgical techniques and other therapeutic options perform relative to each other (e.g., see references[17-22]). None of the over 30 systematic reviews and meta-analyses (e.g., see references[23-30]) on this topic to date includes all treatment modalities for both BCC and SCC. The Australian and Finnish clinical practice guidelines for keratinocyte carcinoma management allude to the difficulty in interpreting the existing evidence-base, which comprises comparisons among pairs of several available treatments.[31, 32] Furthermore, existing guidance is not based on systematic assessments of the evidence. It is hoped that the information in this review will be useful in the development of future guidelines, such as the guidelines on keratinocyte carcinomas from the American Academy of Dermatology, anticipated later in 2016.

Interventions for treating skin cancers differ substantially in cost and have a huge economic impact.[3, 8, 33, 34] Payers are faced with increased utilization of costly therapies, such as brachytherapy, without clear evidence for relative benefits to justify increased costs.[35]

Estimates of keratinocyte carcinoma treatments' comparative effectiveness and safety with respect to patient-relevant outcomes are needed to inform clinical decisionmaking and payer coverage decisions. The objective of this systematic review is to comprehensively collect and synthesize information on the comparative effectiveness and safety of each of the above-mentioned therapeutic strategies for both BCC and SCC.

The Key Questions

The review addresses two key questions for adult patients with basal cell or squamous cell carcinoma of the skin. Each key question will be answered separately for SCC and BCC:

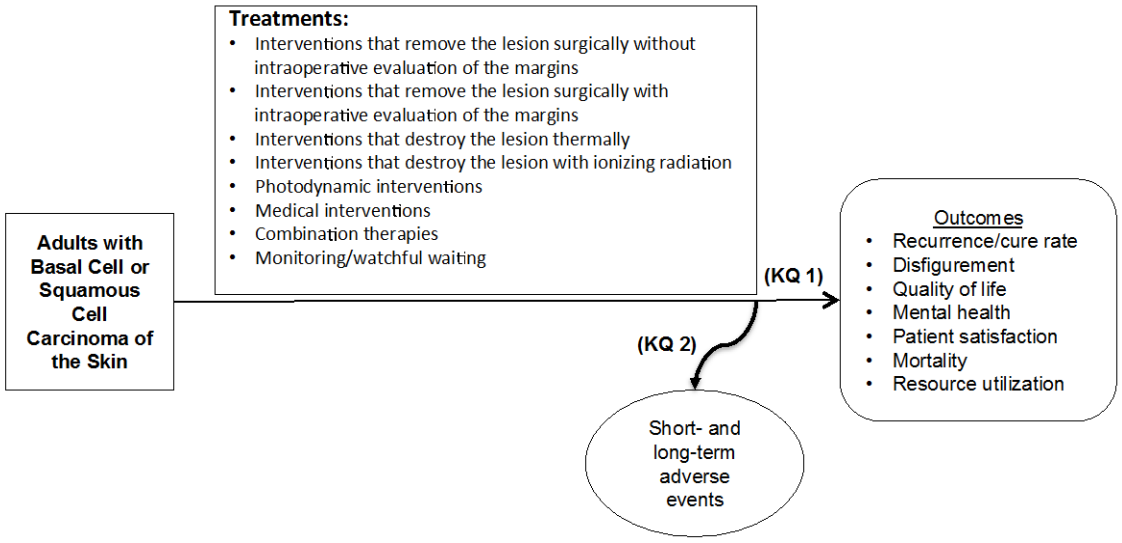
Key Question 1: What is the comparative effectiveness of various interventions, overall and in subgroups of interest?

Key Question 2: How do the adverse events associated with the various interventions compare overall and in subgroups of interest?

The Analytic Framework

The analytic framework in Figure 1 depicts the chain of logic that evidence must support to link the studied interventions.

Figure 1: Analytic Framework for Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin



Methods

The Brown Evidence-based Practice Center (EPC) conducted this review based on a systematic review of the published scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[36] The Prospero registration number is CRD42016043353.

Eligibility Criteria

We use the Population, Intervention, Comparator, Outcomes, and Designs (PICOD) formalism to define the characteristics of the eligible studies for this review.

Population

The population of interest is people with primary squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). This specifically excludes recurrent or metastatic disease. If populations were mixed, we included studies with at least 80 percent primary, non-metastatic BCC or SCC. We excluded studies of recurrent or metastatic cancers in which it was not clear whether the advanced lesions were less than 20 percent of the total lesions studied.

We were also interested in the following specific sub-populations: (1) people who are immunocompromised, including those who have had a solid organ or bone marrow transplant, human immunodeficiency virus (HIV), chemotherapy, Chronic Lymphocytic Leukemia (CLL) or other leukemias and lymphomas, or other iatrogenic; (2) people with a limited life expectancy (e.g., the very elderly, those with terminal cancer, those with end stage renal disease). We have excluded sub-populations based on rare genetic factors (e.g., basal-cell nevus syndrome and xeroderma pigmentosa).

In addition, we were interested in the effects of treatments in subgroups as defined by location (e.g. face, hands, trunk, or extremities) and grade of lesion (e.g. superficial or nodular BCC or SCC in situ [Bowen's Disease] in SCC).

Interventions

The interventions of interest are organized into intervention categories (A through J):

K.	Surgical excision without intraoperative evaluation of the margins
L.	Surgical excision with intraoperative evaluation of the margins Mohs micrographically controlled surgery Surgery with examination of frozen sections
M.	Interventions that destroy the lesion via temperature gradients (C1) Cryotherapy (C2) Diathermy/electrodesiccation (C3) Curettage of the lesion plus diathermy (cauterization) of margins (C4) Curettage of the lesion plus cryotherapy (C5) CO_2 laser therapy
N.	Interventions that destroy the lesion with ionizing radiation (D1) External beam radiation with photons (X or gamma rays), electrons (beta

	rays), or positively charged particles (e.g., protons, helium nuclei/alpha rays), at orthovoltage or megavoltage energies, or using in-office radiation machines (eg. SENSUS machines (gamma rays only) (D2) Brachytherapy with superficial application or interstitial application (pleisiotherapy) of radiation sources (usually emitting beta or alpha rays)
O.	Photodynamic interventions (E1) 5-aminolevulinic acid (ALA) + blue light (E2) Methyl aminolevulinate (MAL) + red light (E3) Other forms of PDT
P.	Medical interventions (F1) 5-fluorouracil (5-FU) (F2) Imiquimod (F3) Interferon (IFN alpha-2a/2b or INF beta) (F4) Ingenol mebutate (F5) Other medical interventions, including BEC-5 cream, Bleomycin, Methotrexate, Diclofenac, and Hedgehog inhibitors (Vismodegib, Sonidegib)
Q.	Shave excision
R.	Curettage without diathermy
S.	Placebo
T.	No treatment

Outcomes

We evaluated the outcomes in the following list. We did not use strict *a priori* definitions of the outcomes, but included all reported outcomes as defined by study researchers. We evaluated outcomes at any and all time points given in a specific study. We used our best judgment to categorize outcomes when studies failed to clearly define their reported outcomes.

- Recurrence/cure rate (as defined in studies)
- Disfigurement/cosmetic outcome
- Quality of Life (only if they use validated instruments to measure – e.g. Short Form Health Survey-36, Skindex, Skin Cancer Index, Skin Cancer Quality of Life Impact Tool)
- Mental health, anxiety, depression, intrusive thoughts (only if they use validated instruments to measure – e.g. State-Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, Impact of Event Scale)
- Patient satisfaction with treatment (only if they use validated instruments to measure – e.g. Patient Satisfaction Questionnaire-18, Skin Cancer Index patient satisfaction subscale)
- Mortality
- Adverse events, including those that are reported by patients and clinically, as well as actively and passively. Both short-term (e.g. pain, skin irritation) and long-term (e.g. radiation exposure, scarring) adverse events were recorded. We systematically reviewed the following endpoints: “any serious adverse event” (leading to treatment discontinuation, or as defined by each study), “pain” and “infection”. We enumerated the set of other reported events.

Design

We evaluated all randomized controlled studies and all comparative non-randomized controlled studies. We excluded studies enrolling fewer than 10 people total because they were unlikely to yield precise or broadly applicable conclusions. We excluded non-English studies, as there were very few of them and there is empirical evidence that excluding them typically has minimal impact on conclusions.[37] Studies in any setting were acceptable.

As described by Linos et al.,[16] patient treatment is often determined by factors, such as disease stage, medical history, age and education, that could confound assessment of the outcomes of interest. Thus for the non-randomized comparative studies (NRCSs), we required that studies included an analysis that accounted for confounders, such as inclusion in a multivariate model, balancing or quasi-randomization, or clearly matched groups. NRCSs that report only crude results were identified and tabulated but were excluded from the analysis in the full report.

Evidence Identification

We conducted literature searches of studies in PubMed, the Cochrane Central Trials Registry, the Cochrane Database of Systematic Reviews, and EMBASE to identify primary research studies meeting our criteria through June 2016. These databases should adequately cover the published literature on this topic. The full search strategy for all databases is in Appendix A. We screened all references in published clinical practice guidelines, relevant narrative and systematic reviews, and Scientific Information Packages from manufacturers or other stakeholders. We searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing studies and studies that are not published in the medical literature. In addition, we searched the FDA drugs and devices portals for unpublished data. We did not find any studies with results that were not included in the published literature. Our requests to manufacturers for scientific information packets also did not yield any new data. We have extracted and incorporated all studies de novo and have not summarized or incorporated existing systematic reviews, per se. All articles identified through these sources have been screened for eligibility, using the same criteria as was used for articles identified through literature searches. The search will be updated upon submission of the draft report for peer and public review.

All citations found by literature searches and other sources were independently screened by two researchers. At the start of abstract screening, we implemented a training session, in which all researchers screened the same articles and conflicts were discussed. During title and abstract double-screening, we resolved conflicts as a group. All title and abstract screening was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/).[38] All potentially relevant studies were rescreened in full text with double-screening to ensure eligibility.

Data Extraction and Data Management

Each study has been extracted by one member of the review team, which includes clinicians and methodologists. The extraction was reviewed and confirmed by at least one other experienced methodologist. Any disagreements were resolved by discussion among the team. Data was extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the Key Questions. Upon completion of the review, the SRDR database will be made accessible to the

general public (with capacity to read, download, and comment on data). The basic elements and design of the extraction form are the similar to those used for other AHRQ comparative effectiveness reviews and include elements that address population characteristics, including method of diagnosis; descriptions of the interventions, exposures, and comparators analyzed; outcome definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias questions. If information was stratified by carcinoma subtype for BCC (e.g. superficial or nodular) and SCC (e.g. SCC in situ, well-differentiated, or poorly differentiated), we recorded that information as well.

Assessment of Methodological Risk of Bias of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[39] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used relevant questions from the Newcastle Ottawa Scale.[40] For RCTs, the review team discussed each article, based on methodological (design and analysis) items that are related to the aforementioned biases for each outcome of each trial. To obtain information on (a lower bound of) the number of yet unpublished trials, we searched clinicaltrials.gov for completed trials, and examined the publication status of thus identified studies.

Data Synthesis

All included studies were summarized in narrative form and in summary tables that include the important features of the study populations, design, intervention, outcomes, and results. Lesions were divided by subtype (superficial, nodular, or high-risk BCC, SCC, or mixed populations) for analysis to ensure that the treatments would be most comparable. Where possible, lesions were also evaluated by size and location. Arms with fewer than 5 lesions were not included in the analysis, because they contribute minimal information, and in some instances, necessitated adding model parameters that were difficult to estimate.

We conducted pairwise and network meta-analyses with mixed effects (random intercepts and fixed intervention slopes) or full-random effects (random intercepts and random slopes) multilevel models within the generalized linear and latent mixed models. We used the normal approximation to discrete likelihoods with a canonical (logit) link function. Treatment effect estimates from such models are odds ratios. We fit models by maximizing the restricted likelihood. We explored clinical and methodological heterogeneity in subgroup analyses. We did not conduct dose-response meta-analyses because there was substantial heterogeneity in the definitions of intervention intensity (dose) across studies; instead, we summarized dose-response results qualitatively. To aid the interpretation of these analyses we also present model-based estimates for the mean frequency of an outcome in the examined interventions, as well as forecasts of the frequency of the outcome in a new setting (e.g., anew study, or in a population) that is similar to the studies in the meta-analysis. The forecasts' point estimate about the frequency of the outcome is very close to the point estimate of the mean frequency of the outcome over the meta-analyzed studies. However, the 95% confidence interval (CI) for a forecast of the frequency of an outcome in a new setting accounts for between-study

heterogeneity, and will, thus, be broader than the corresponding 95% CI for the mean frequency of the outcome across the analyzed studies. See the next paragraph about the presentation of results. Inconsistency was assessed by comparing the fit of models that do not assume consistent intervention effects versus typical network meta-analysis models, that assume consistent treatment effects. Analyses did not identify statistical evidence of inconsistency. Because such analyses are known to be underpowered, we also compared qualitatively the agreement of estimates based only on direct data versus of estimates based on both direct and indirect data. Such estimates were deemed to be congruent.

Presentation of results

We present results with plots and tables. We briefly describe three expository formats that are not commonly used in EPC reports, namely, evidence graphs, league tables, and relative effects tables.

Evidence graphs

We use evidence graphs such as the one in Figure 2 to describe which interventions have been compared with others. An evidence graph comprises nodes, which represent interventions, and edges (depicted by a line linking nodes). Edges connect a pair of nodes only if the corresponding interventions have been compared in at least one head-to-head study. In Figure 2, nodes for interventions from the same intervention category are in a shaded area. For example, nodes E1 (corresponding to PDT with MAL) and E2 (corresponding to PDT with ALA) are within the same shaded area which represents PDT as the type of intervention), and analogously for other nodes and interventions in the Figure. The organization of interventions in intervention categories has been described in the Interventions paragraph. We use the term *connected subgraph* to describe a set of nodes that are connected through one or more edges. For example, Figure 2 has 2 connected subgraphs, which include the following nodes:

1. A|B, D1|D2, and
2. all remaining nodes in the evidence graph, namely A, B, A|B, B+F3, D1, F2, H, C3, C4, C1, C5+E1, E1, and E2.

If all the nodes in the graph were connected, then there would be a single connected subgraph—which would be the whole graph. Identifying connected subgraphs is important, because we do not statistically compare interventions that belong to different connected subgraphs.

Figure 3 is an analogous representation of the comparisons between intervention categories for the same network of interventions depicted in Figure 2. When one considers intervention categories, comparisons between interventions that belong to the same type are not pertinent. Such comparisons are represented by edges enclosed in the shaded areas in the evidence graph in Figure 2. Observe also that comparing between intervention categories happened to result in a single connected subgraph in Figure 3.

Figure 2: Example evidence graph depicting comparisons between individual interventions.

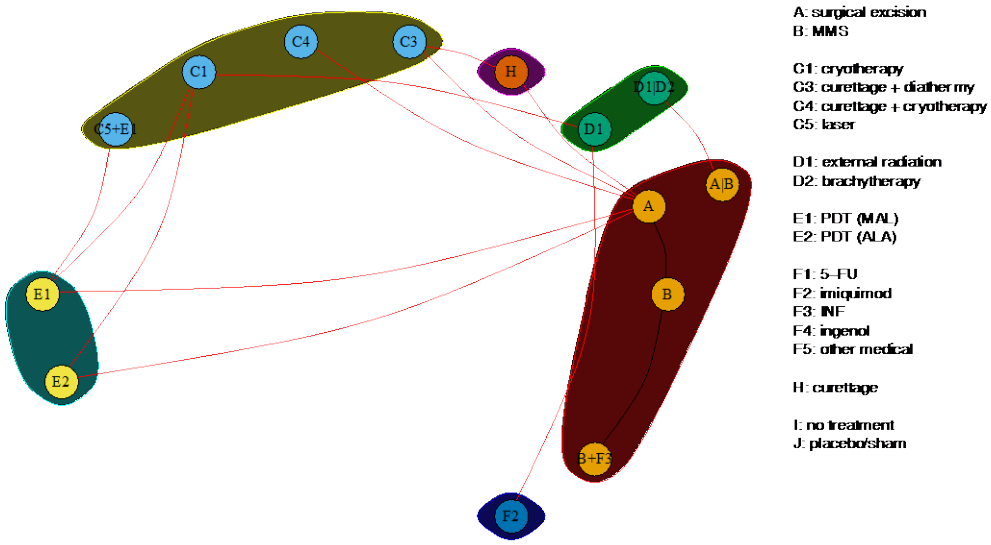
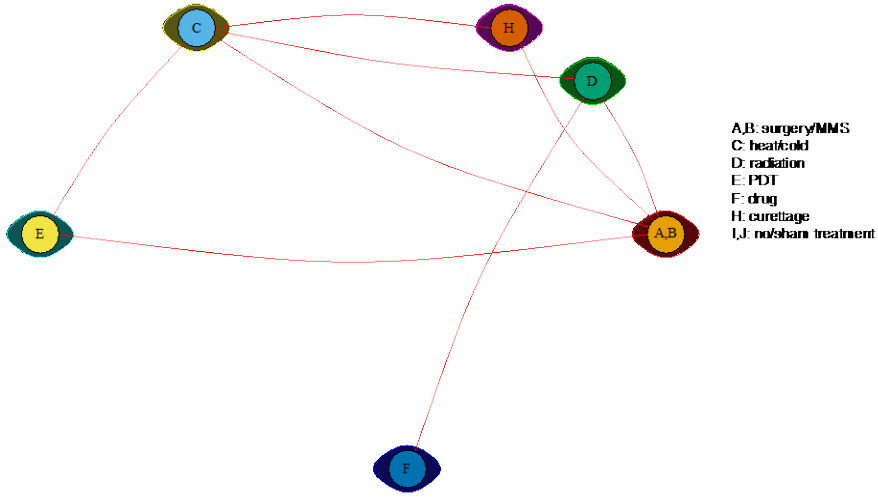


Figure 3: Evidence graph depicting comparisons between intervention categories.



Relative effects tables

Relative effects tables describe odds ratio estimates and 95% CIs for all pairwise comparisons in a connected subgraph. Table 1 is an example; it is the analysis that corresponds to the evidence graph in Figure 3. Each cell has a (row, column) address, and reports the estimated odds ratio between the intervention in the row versus the intervention in the column. Consider the cell in the second row, fourth column: The odds ratio comparing interventions that destroy lesions with heat or cold (with code letter C; the intervention in the row) versus PDT (E; the intervention in the column) was 0.91 (95% CI, 0.43 to 1.95). The cell in the *fourth* row, *second* column is the odds ratio for a comparison between the same interventions but in the other direction: 1.10 (95% CI, 0.51, 2.34) is the odds ratio of PDT (E) versus interventions that destroy the lesion with heat or cold (C). The unshaded cells correspond to comparisons for which there is head-to-head information, i.e., there is an edge between these corresponding nodes in the

evidence graph. The estimated treatment effects in these cells are informed by direct and indirect evidence. The shaded cells correspond to comparisons that have not been empirically observed (there is no edge between these corresponding nodes in the evidence graph), and are based only on indirect comparisons.

Table 1. Relative odds ratios for an outcome between intervention categories

surgery/MMS (A,B)	0.13 (0.05, 0.35)	0.77 (0.22, 2.73)	0.12 (0.04, 0.32)	1.09 (0.05, 24.23)	0.14 (0.03, 0.77)
7.71 (2.83, 20.98)	Heat/cold (C)	5.95 (2.03, 17.4)	0.91 (0.43, 1.95)	8.44 (0.41, 173.75)	1.09 (0.23, 5.16)
1.3 (0.37, 4.59)	0.17 (0.06, 0.49)	Radiation (D)	0.15 (0.05, 0.45)	1.42 (0.06, 32.2)	0.18 (0.03, 1.04)
8.45 (3.08, 23.16)	1.10 (0.51, 2.34)	6.52 (2.21, 19.21)	PDT (E)	9.25 (0.45, 190.91)	1.19 (0.25, 5.68)
0.91 (0.04, 20.24)	0.12 (0.01, 2.44)	0.7 (0.03, 15.99)	0.11 (0.01, 2.23)	drugs (F)	0.13 (<0.005, 3.56)
7.08 (1.3, 38.49)	0.92 (0.19, 4.35)	5.46 (0.96, 31.02)	0.84 (0.18, 3.99)	7.75 (0.28, 214.11)	Curettage (H)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy. This example is for analyses of recurrence among patients with BCC lesions.

League tables

League tables such as Table 2, describe the mean fraction of lesions with the outcome of interest for each intervention (or intervention catgory) over the populations included in the meta-analysis, and the corresponding forecasted fraction in a new setting that is analogous to the settings of the analyzed studies. The results in the league table and the results in the relative effects table are from the same analysis. The league table explains what the relative effects imply about the probability of the outcome under each treatment. In the example, over the meta-analyzed studies the probability of the event with PDT (E) was 23.0 percent (95% CI 14.8 to 33.9) and with interventions that destroy the lesion with heat or cold (C) it was 21.4 percent (95% CI 13.8 to 31.6). The expected frequency of the event in a setting that is analogous to the settings in which the meta-analyzed studies where conducted is shown in the forecast column. Note that the confidence intervals for the forecast are always larger than the confidence intervals for the mean.

Imagine that you are hiking along a trail from east to west, through six camp sites. The camp sites serve as the analogue for the interventions. A table showing the signed distances[1] between pairs of campsites would be the analogue of the relative effects table. A table showing how far each campsite is from the easternmost end of the trail would be the analogue of the league table.

[1] A signed distance encodes the direction of movement and the distance traveled.

Table 2. Mean and forecasted event fractions by intervention catgory, based on the relative effects in Table 1.

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
Surgery/MMS (A,B)	3.4 (1.5, 7.6)	3.4 (1.0, 11.4)
Heat/cold (C)	21.4 (13.8, 31.6)	21.4 (8.3, 45.1)
Radiation (D)	4.4 (1.8, 10.4)	4.4 (1.2, 15.0)
PDT (E)	23.0 (14.8, 33.9)	23.0 (8.9, 47.5)
Drugs (F)	3.1 (0.2, 38.8)	3.1 (0.1, 42.5)
Curettage (H)	20.0 (5.5, 51.9)	20.0 (4.1, 59.1)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We graded the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[36] We assed the strength of evidence for each outcome. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we have assigned a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating are summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating.

We assessed the applicability within and across studies with reference to demographics of enrolled participants (e.g. age and sex distributions), the location and severity of the lesions, and the availability of treatments (e.g. with respect to radiation treatments).

Peer Review

A draft version of this report will be reviewed by invited and public reviewers. Revisions of the draft will be made, where appropriate, based on their comments. The draft and final reports will also be reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

Summary of Studies

The literature searches yielded 14588 citations (Figure 4), of which 14165 were excluded in abstract screening. A search of the reference lists of relevant systematic reviews yielded another 85 studies, which brought the total number screened in full text to 508. Appendix A presents the literature search strategies (for each searched database). Appendix B lists the articles that were reviewed in full text that were excluded, with their rejection reasons.

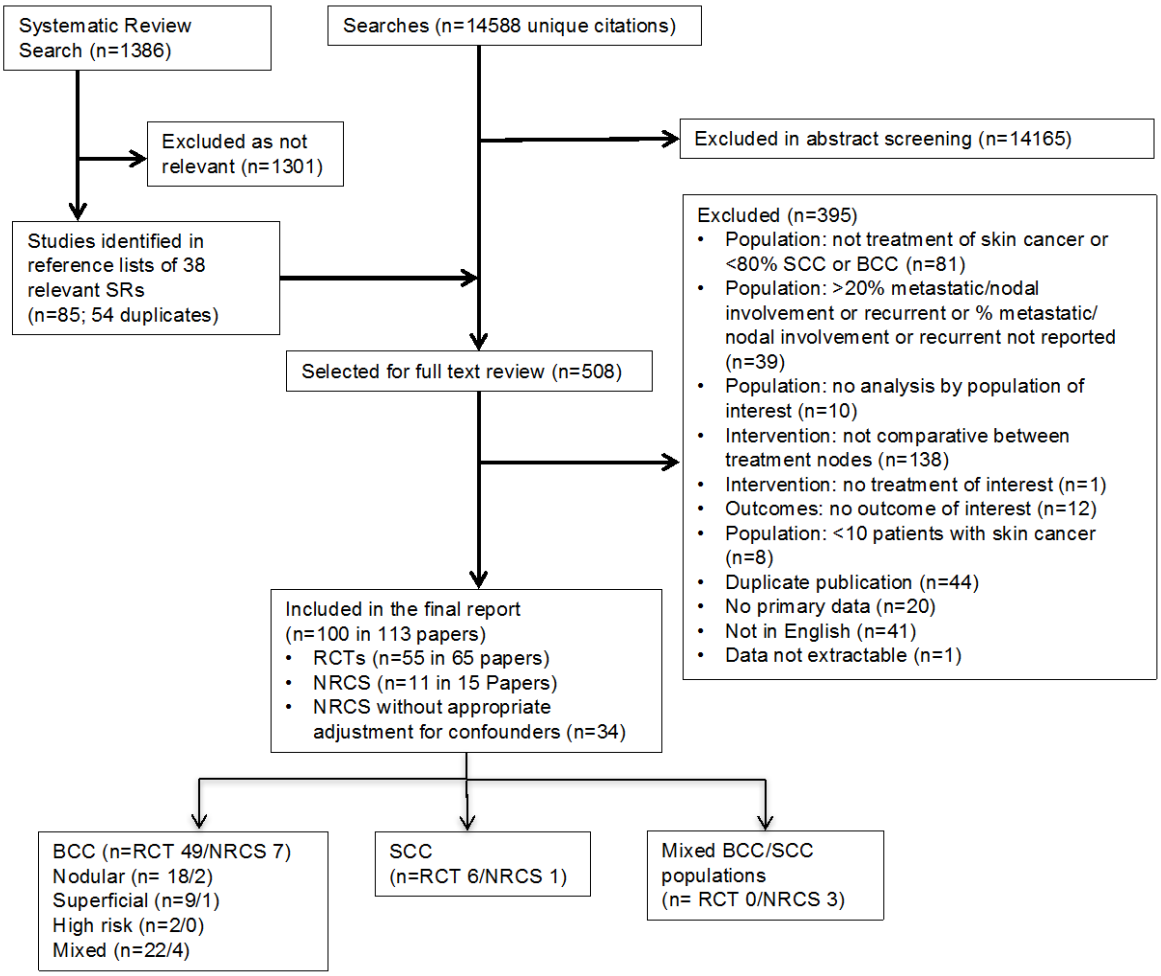
The 101 included studies (described in 113 papers) report 55 randomized controlled trials (RCTs) and 45 non-randomized comparative studies (NRCSs). Two papers reported the results of two separate trials and were analyzed separately; another seven studies were reported in multiple papers. Among the 55 RCTs in 64 papers,[18, 19, 21, 41-101] 54 were reported in full papers, and two were reported only as conference abstracts.[41, 60]Eighteen reported industry funding[50, 52, 62, 64, 65, 70, 71, 75, 79, 81, 88, 90, 92-94, 96, 100], 5 used materials supplied by industry,[48, 51, 57, 58, 101] 15 explicitly reported no industry support,[18, 45, 47, 49, 53-55, 66, 68, 69, 72, 77, 87, 95, 98] and 18 did not provide funding information[19, 41-44, 46, 59, 60, 63, 67, 76, 78, 85, 86, 89, 97] (Appendix C).

Eleven of the NRCS contained either matched cohorts or adjustments for known confounders, and they were included in the analysis; the remaining 34 have been tabulated in Appendix H[102-136] Of the 11 NRCSs in 15 papers.[137-151] 2 reported industry funding,[139, 149] 6 explicitly reported no industry support,[138, 140-144, 146-148, 151] and 3 did not provide funding information[137, 145, 150] (See Appendix C). Results from NRCSs are presented at the end of each outcome section.

The studies primarily reported on Basal Cell Carcinoma (BCC), with a minority reporting results for Squamous Cell Carcinoma (SCC). Nearly all reported results for recurrence or cure rate outcomes and adverse events, and many reported results for cosmetic outcomes. Few studies reported results using validated instruments for quality of life, mental health, or patient satisfaction with treatment. Details about study design, baselines, and treatments are in Appendix C, D, and E, respectively. Risk of bias assessments are shown in Appendix F.

Because of the wide variety of adverse events reported (see Appendix H for a list of adverse events and how many studies reported each), we have limited the analysis to (i) adverse events that lead to treatment discontinuation, (ii) any serious or severe adverse event (as defined by each study), (iii) infections of the treatment site, and (iv) pain after treatment.

Figure 4. Literature Flow Diagram



Studies that enrolled both BCC and SCC populations are discussed in the BCC sections, because most enrolled lesions were BCCs.

Basal Cell Carcinoma (BCC)

The evidence graph in Figure 5 shows that there are 35 comparisons that have been observed between 28 interventions organized in 7 intervention categories.
This evidence graph suggests that limited conclusions can be drawn about which individual intervention is best (with respect to each outcome) for two reasons: 1) some interventions have never been compared with other interventions, directly or indirectly, and 2) the observed comparisons between individual interventions are relatively sparse.

Groups of interventions that have never been compared with other groups are readily identified in the Figure, because they are represented as connected subgraphs. For example, one connected subgraph comprises radiation therapy (external or brachytherapy, node D1|D2) versus surgery (surgical excision or Mohs micrographic surgery, node A|B). Another connected subgraph comprises laser ablation (C5) versus diclofenac and/or calcitriol (other medication – F5) and versus no treatment (I). Four such subgraphs exist, and no conclusions can be drawn between interventions that belong to different subgraphs.

For individual interventions, the observed comparisons are relatively sparse: there are only 35 observed comparisons in the Figure, out of the 378 that are possible among the 28 treatments. Further, information on each comparison is provided by at most three RCTs, and for most comparisons by only a single RCT. The evidence is even more sparse when one considers the information that is actually available for specific outcomes. Figure 6 shows the evidence graphs for the outcomes for which we have the most data, namely recurrence, lack of histologic clearance, and lack of clinical clearance. For these outcomes, no RCT data exist for 14, 8, and 14 of the 28 interventions, respectively. Evidence on other outcomes (quality of life, cosmetic outcomes, and costs or resource use) is even more sparse, as discussed in the following sections.

The evidence remains sparse at the level of individual interventions even after considering results from the seven eligible NRCSs, which are described separately from the RCTs.

Figure 5: Evidence graph depicting compared treatments in RCTs of BCC lesions.

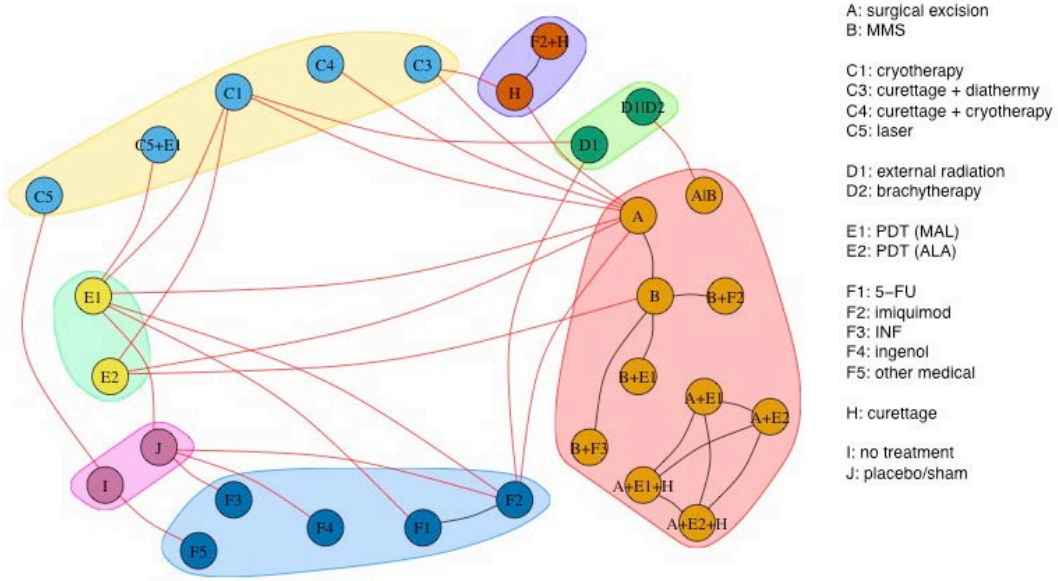
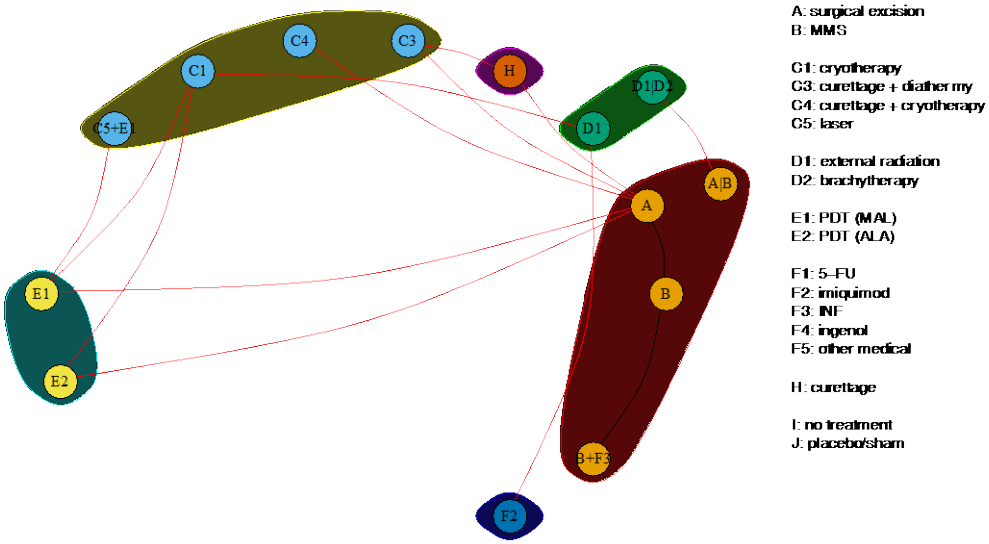
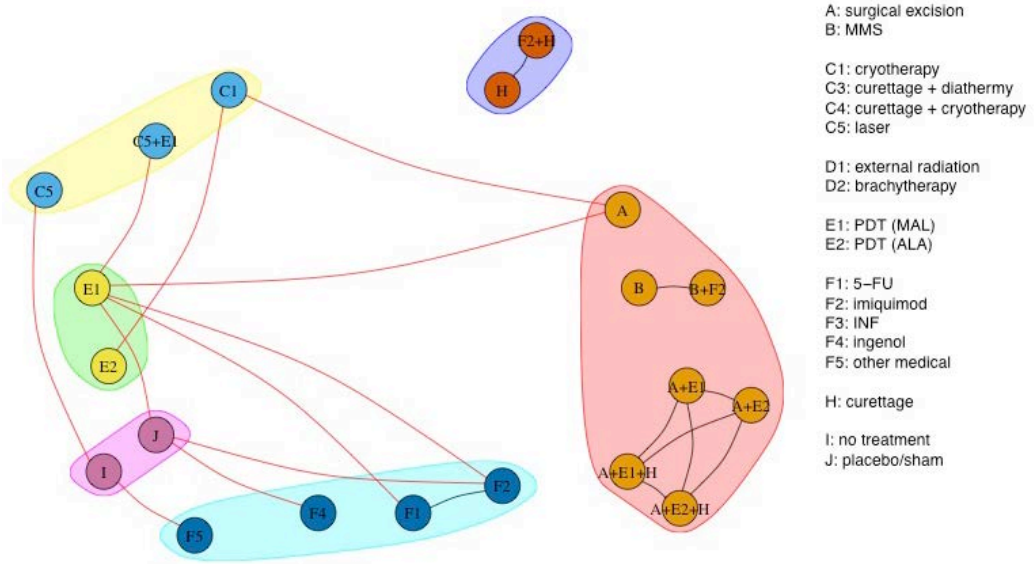


Figure 6: Evidence graphs for recurrence, histologic clearance and clinical clearance from RCTs of BCC lesions

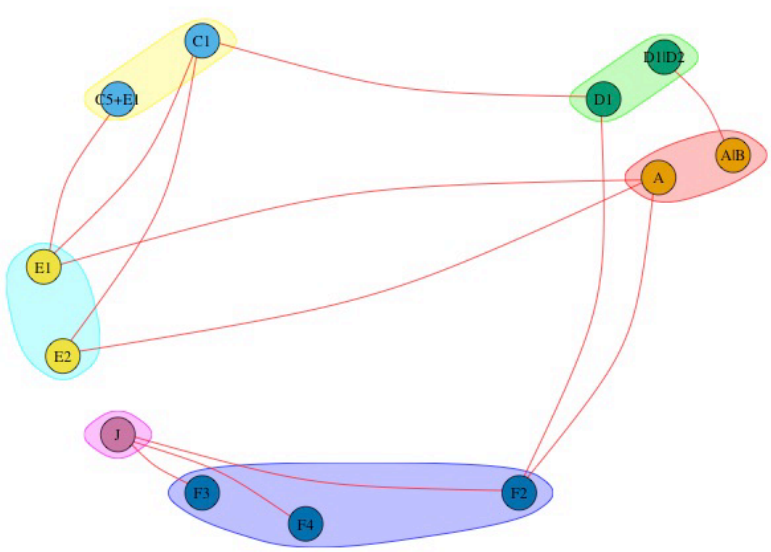
(A) Recurrence



(B) Lack of histologic clearance



(C) Lack of clinical clearance



A: surgical excision
B: MMS

C1: cryotherapy
C3: curettage + diathermy
C4: curettage + cryotherapy
C5: laser

D1: external radiation
D2: brachytherapy

E1: PDT (MAL)
E2: PDT (ALA)

F1: 5–FU
F2: imiquimod
F3: INF
F4: ingenol
F5: other medical

H: curettage

I: no treatment
J: placebo/sham

The characteristics of the included RCTs are summarized in Tables 3 through 6, for RCTs on superficial (n=9), nodular (n=18), high-risk (n=2), and mixed types (n=22) of BCC lesions. RCTs that report stratified results for different types of lesions are listed in the mixed table.

Across all trials, the mean or median age of enrollees ranged between 55 and 75.3 (median: 64, 25^{th}-75^{th} percentile: 61 to 67). The proportion of female patients ranged between 0 and 75 percent (median: 37, 25^{th}-75^{th} percentile: 30 to 43). When reported, the mean or median lesion area was between 30.1 and 205 mm^2, and the median maximum diameter was between 5.3 and 12 mm. The majority of RCTs included lesions in various body locations, and only a few reported results stratified by lesion location (discussed separately). Based on this information, the RCTs included patients and lesions are typically encountered in clinical practice, but the lack of information on treatment effect heterogeneity with respect to patient-level factors hinders extrapolation to specific patient subgroups. No RCT focused on patients who were immunocompromised or had substantially limited life expectancy.

In terms of design characteristics, 29 RCTs had two arms, 5 had three arms, and 15 had four or more; the latter were primarily phase II studies, examining the tolerability of various doses or schedules of topically applied medications or alternative photodynamic treatment protocols. Such phase II studies are included in the comparisons between interventions only when they include a no intervention or placebo/sham intervention arm. Their findings with respect to different doses or protocols for the same intervention are summarized separately. Analyzed sample sizes ranged between 18 and 694 (median: 70, 25^{th}-75^{th} percentile: 31 to 126.5); sample sizes per RCT arm ranged between 3 and 408.

Based on what was reported in the RCTs, we deemed that the allocation sequence was randomized using formal methods in 26 and successfully concealed in 25 RCTs, and that patients, providers, and outcome assessors were successfully blinded to the received treatments in 19, 13, and 19 RCTs, respectively. Our consensus assessment of the reported baseline characteristics across the compared arms in each RCT was that most RCTs (n=28) had arms that were likely balanced at baseline. In 41 RCTs fewer than 20 percent of patients had missing outcomes for any eligible outcome in any arm.

Table 3. Characteristics of RCTs of superficial BCCs.

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
Arits 2013 23683751	MAL-PDT	median 63	52	NR	head/neck excluding H-zone (12), extremities (29), trunk (59), upper extremities (16), lower extremities (13)	Yes	Yes	Yes	No	No	Yes	Yes
	Imiquimod	median 62	49	NR	head/neck excluding H-zone (12), extremities (27), trunk (61), upper extremities (13), lower extremities (14)							
	Fluorouacil	median 64	47	NR	head/neck excluding H-zone (15), extremities (24), trunk (60), upper extremities (13), lower extremities (11)							
Basset-Seguin 2008 18693158	MAL-PDT	62	33	NR	face/scalp (6), extremities (22), trunk/neck (72)	No	Yes	Yes	No	No	Unsure	Yes
	Cryotherapy	64	47	NR	face/scalp (4), extremities (20), trunk/neck (76)							
Beutner 1999 10570388	imiquimod 3x/week	NR	NR	NR	upper extremity (25), anterior upper trunk (25), posterior upper trunk (25), neck (25)	No	No	No	Unsure	Yes	Unsure	Yes
Geisse 2002	Imiquimod	62	NR	median 1.0 cm^2	neck/face/forehead (4), upper	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
12196749	3x/wk				extremity (not hand) (15), trunk (73), lower extremity/thigh (not foot) (8)							
	Imiquimod 5x/wk	55	NR	median 0.6 cm^2	neck/face/forehead (3), upper extremity (not hand) (31), trunk (55), lower extremity/thigh (not foot) (10)							
	Imiquimod 1x/day	56	NR	median 0.7 cm^2	neck/face/forehead (7), upper extremity (not hand) (21), trunk (64), lower extremity/thigh (not foot) (7)							
	Imiquimod 2x/day	69	NR	median 1.0 cm^2	neck/face/forehead (8), upper extremity (not hand) (54), trunk (31), lower extremity/thigh (not foot) (8)							
	vehicle (control)	58	NR	median 0.8 cm^2	neck/face/forehead (9), upper extremity (not hand) (34), trunk (47), lower extremity/thigh (not foot) (9)							
Schleier 2007 25047438	ALA-thermogel PDT	69.9	46.15	NR	face (54.17), scalp (20.83), lip (2.78), eyelid (1.39), extremities (9.72), trunk/neck (11.11)	Yes	No	Yes	Yes	Yes	Yes	Yes

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
	Methyl-ALA-thermogel PDT	71.8	36.36	NR	face (52.5), scalp (30), extremities (5), trunk/neck (12.5)							
Schulze 2005 15888150	imiquimod 5%	64.3	39	NR	cheek (1), forehead (0), extremities (including hand) (20), trunk/neck (70)	Yes	Yes	Yes	Yes	No	Unsure	No
	vehicle	64.5	39	NR	cheek (1), forehead (5), scalp (1), extremities (including hand) (30), trunk/neck (61)							
Siller 2010 20546215	Total (ingenol mebutate vs placebo)	59	27	9 mm	NR	Yes	Yes	Yes	Yes	Yes	Yes	Unsure
Sterry 2002 12452875 (superficial)	Imiquimod (2 days/ week) with occlusion	63	33	median 1.5 cm^2	extremities (29), trunk/neck (71)	Yes	Yes	No	No	No	Unsure	Yes
	Imiquimod (3 days/ week) with occlusion	58	35	median 1.2 cm^2	extremities (31), trunk/neck (69)							
	Imiquim	69	33	median	face (8).							

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
	od (2 days/ week) without occlusion			1.0 cm^2	extremities (30), trunk/neck (62)							
	Imiquimod (3 days/ week) without occlusion	61	44	median 1.0 cm^2	extremities (32), trunk/neck (64), genitals (4)							
Szeimies 2008 18624836	MAL-PDT	64.5	36.0	12.5 mm	face/scalp (11.1), extremities (28.9), trunk/neck (60)	Yes	Yes	Yes	No	No	No	Yes
	excision	63.1	31.3	12.6 mm	face/scalp (4.5) , extremities (25.0), trunk/neck (70.5)							

*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm.

Table 4. Characteristics of studies of nodular BCC.

Study	Arm	Age, mean	female, %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
Abbade 2015	Surgical excision	NR	NR	NR	head and neck (100)	No	No	Yes	No	No	unsure	Yes
	MAL-PDT	NR	NR	NR	head and neck (100)							
Al-Niaimi 2015 26157307	PDT + MMS	61.4	66.7	200 mm^2	face (100)	No	Yes	Yes	No	No	Yes	No
	MMS	62.7	40	201 mm2	face (100)							
Berroeta 2007 17573890	Total (PDT vs. excision)	median 72	NR	NR	NR	Yes	Yes	unsure	No	No	Yes	Yes
Butler 2009 19018814	Vehicle group+MOHs	75.3	43.8	30.1 mm2	face (100)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	imiquimod 5% Cream group+MOHs	73.3	66.7	33.5 mm2	hands (100)							
Choi 2016 26551044	Er:YAG ablative fractional laser-primed MAL- PDT	NR	55	NR	NR	No	Yes	Yes	Yes	Yes	Yes	Yes
	MAL-PDT	NR	36.8	NR	NR							
Eigentler 2007 17610993	imiquimod 5% 8 weeks	median 65	27	8.2 mm	face (24.4), scalp (2.2), ear (8.9), trunk/neck (4.4), perioral (4.4), periorbital (8.9), nose (42), arm/shoulder (4.4)	No	No	Unsure	No	unsure	unsure	Yes

Study	Arm	Age, mean	female, %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
	imiquimod 5% 12 weeks	median 63	33	9.6 mm	face (19.6), scalp (2.2), ear (10.9), trunk/neck (8.7), perioral (2.2), periorbital (6.5), nose (37), arm/shoulder (4.4), leg/hip (4.3)							
Foley 2009 20064185	methyl-aminolevulinatePDT	66	28.78	8.8 mm	face/scalp (25), extremities (20), Trunk 32 (43%) Neck 9 (12%)	Yes	Yes	unsure	Yes	Yes	Yes	Yes
	placebo PDT	67	20	9.0 mm	face/scalp (31), extremities (23), Trunk 34 (45%) Neck 1(1%)							
Haak 2015 24903544	MAL PDT	NR	37.5	median 8.5 mm	nose (37), forehead (31), cheek (6), oral area (13), periorbital area (13)	Yes	Yes	Yes	No	No	Yes	Yes
	AFXL MAL PDT	NR	68.8	median 7 mm	nose (56), forehead (19), cheek (13), oral area (6), periorbital area (6)							
Kuijpers 2006 16865869	ALA-PDT (total)	68.4	34.9	8.1 mm	forehead/temple+nose/parana	Yes	Yes	unsure	No	No	Unsure	No

Study	Arm	Age, mean	female, %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
					sal (36.4), cheek/chin/lips (9.1), ears (9.1), extremities (9.1), trunk/neck (36.4)							
	MAL-PDT (total)	68.4	34.9	8.4 mm	forehead/temple+nose/paranasal (38.1), cheek/chin/lips (4.8), ears (14.3), extremities (4.8), trunk/neck (38.1)							
	ALA-PDT (debulking subgroup)	68.4	34.9	NR	NR							
	ALA-PDT (no debulking subgroup)	68.4	34.9	NR	NR							
	MAL-PDT (debulking subgroup)	68.4	34.9	NR	NR							
	MAL-PDT (no debulking subgroup)	68.4	34.9	NR	NR							
Kuijpers 2007 17451581	Curettage + Cryosurgery	67	43	5.4 mm	Forehead/temple, Cheek/chin, Periocular (80), Lips/mouth (4), Ears/periauricu	No	No	Yes	Unsure	Unsure	Yes	Yes

Study	Arm	Age, mean	female, %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
					lar (8), Neck, chest/back (8)							
	Surgical excision	67	43	5.3 mm	Forehead/temple, Cheek/chin, Periocular (76), Lips/mouth (6), Ears/periauricular (6), Neck, chest/back (12)							
Mosterd 2008 18717680	ALA-PDT	64	48.2	8.9 mm	face (53); "rest of the body" (47%)	Yes	Yes	Yes	Yes	No	No	No
	Surgical excision	65.1	50	9.3 mm	face (51); "rest of the body" (49%)							
Orenberg 1992 1430394	7.5 mg 5-FU	60	5	123.9 mm^2	face (30), extemities (30), trunk/neck (40)	unsure	unsure	No	yes	yes	yes	Yes
	15 mg 5-FU	60	5	76.4 mm^2	face (10), scalp (10), lip (10), ear (30), extemities (10), trunk/neck (30)							
Rhodes 2004 14732655	MAL PDT	69	38	NR	face/scalp (40), extremities (11), trunk/neck (49)	Yes	Yes	No	No	No	No	No
	excision	67	41	NR	face/scalp (58), extremities (9), trunk/neck (29)							
Shumack 2002	vehicle cream	NR	42	median 0.8	face (17), trunk/neck	No	No	No	Yes	unsure	unsure	Yes

Study	Arm	Age, mean	female, %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
12224978 (12 weeks)				cm^2	(54.2), upper extremity (not hand) (25), lower extremity (not foot) (4)							
	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week	NR	75	median 0.8 cm2	face (25), trunk/neck (75)							
	imiquimod (IMQ) 5% cream - Once daily for 7 days per week	NR	10	median 0.7 cm2	face (29), trunk/neck (33), upper extremity (not hand) (19), lower extremity (not foot) (10)							
	imiquimod (IMQ) 5% cream - Once daily for 5 days per week	NR	35	median 0.7 cm2	face (48), trunk/neck (26), Upper extremity (not hand) (17), lower extremity (not foot) (9)							
	imiquimod (IMQ) 5% cream - Once daily for 3 days per week	NR	30	median 0.7 cm2	face (40), trunk/neck (35), upper extremity (not hand) (20), lower extremity (not foot) (5)							
Shumack 2002 12224978 (6 weeks)	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week	NR	0	median 0.6 cm2	face (100)	Yes	unsure	No	Yes	unsure	unsure	Yes

Study	Arm	Age, mean	female, %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
	imiquimod (IMQ) 5% cream - Once daily for 3 days per week	63	13	median 0.8 cm2	face (28), trunk/neck (11.11), Upper extremity (not hand) (25), lower extremity (not foot) (13)							
	imiquimod (IMQ) 5% cream - Twice daily for 7 days per week	69	13	median 0.8 cm2	face (32), trunk/neck (39), Upper extremity (not hand) (26), lower extremity (not foot) (3)							
	imiquimod (IMQ) 5% cream - Once daily for 7 days per week	66	29	median 0.8 cm2	face (11), trunk/neck (48), Upper extremity (not hand) (26), lower extremity (not foot) (3)							
	imiquimod 5%	NR	40	NR	face (60), ear (10), unspecified other (30)	No	No	Unsure	unsure	unsure	No	Yes
	vehicle	NR	10	NR	face (50), ear (20), unspecified other (30)							
Sterry 2002 12452875 (nodular)	Imiquimod (2 days/week) with occlusion	66	50	median: 0.6 cm2	Face (10), Scalp (1), extremities (2), trunk/neck (9)	Yes	Yes	Yes	No	No	Unsure	Yes
	Imiquimod (3 days/week) with	66	30	median: 0.7 cm2	Face (18), extremities (2), trunk/neck (3)							

Study	Arm	Age, mean	female, %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
	occlusion											
	Imiquimod (2 days/week) without occlusion	67	24	median : 1.0 cm2	Face (9), extremities (1), trunk/neck (10)							
	Imiquimod (3 days/week) without occlusion	66	46	median : 0.6 cm^2	Face (11), extremities (5), trunk/neck (8)							
van der Geer 2012 22385074	Imiquimod + Mohs	69	37	NR	H-zone (57), nose (23), ear 4 (11), scalp + frontal (23), other regions (cheek, temporal, chin) (43)	Yes	Yes	Yes	No	No	No	Yes
	no treatment + Mohs	68	31	median 110 mm^2	H-zone (66), nose (26), ear (17), scalp + frontal (14), other regions (cheek, temporal, chin) (43)							
Wettstein 2013 23566745	Ringer's lactate (control group)	59	26.67	2.5 cm2	nose (46.2), cheek (23.1), frontal (7.7), ear (23.1)	Yes	Unsure	Yes	Yes	Yes	Unsure	Yes
	interferon alpha-2b	59	26.67	3.1 cm2	nose (50), cheek (10), frontal (20), ear (20)							

*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm. NR=not reported.

Table 5. Characteristics of RCTs of high-risk BCC lesions

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
Alpsoy 1996 8708151	IFN alfa-2a	58.7	53	median 2.05 cm2	eyelid (27), nose (13), zygoma (27), forehead (13), cheek (13), trunk (7)	Yes	Yes	Unsure	Yes	Unsure	Unsure	Unsure
	IFN alfa-2b	63.6	53	median 1.82 cm2	eyelid (20), nose (7), zygoma (20), forehead (20), cheek (27), trunk (7)							
	IFN alfa-2a + IFN alfa-2b	60.3	40	median 1.9 cm2	eyelid (20), nose (13), zygoma (27), forehead (13), cheek (20), trunk (7)							
Migden 2015 25981810	Sonidegib 200	median 67	39	NR	head and neck (100)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Sonidegib 800	median 65	36	NR	head and neck (100)							

*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm. NR=not reported.

Table 6. Characteristics of RCTs of mixed types of BCC lesions

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
Allen 1979 298425	cryotherapy	NR	NR	NR	NR	Yes	Yes	Unsure	Yes	Unsure	Unsure	Unsure
	radiotherapy	NR	NR	NR	NR							
Alpsoy 1996 8708151	IFN alfa-2a	58.7	53	median 2.05 cm2	eyelid (27), nose (13), zygoma (27), forehead (13), cheek (13), trunk (7)	Unsure	Unsure	Yes	Unsure	Unsure	Unsure	Yes
	IFN alfa-2b	63.6	53	median	eyelid (20),							

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
				1.82 cm2	nose (7), zygoma (20), forehead (20), cheek (27), trunk (7)							
	IFN alfa-2a + IFN alfa-2b	60.3	40	median 1.9 cm2	eyelid (20), nose (13), zygoma (27), forehead (13), cheek (20), trunk (7)							
Avril 1997 9218740	surgery	66.5	54	11.1 mm	nose (53), cheek, pre- and retroauricular areas (21), eyelids, internal and external eye angles (19), forehead, temple, between eyebrows 36 (21), chin, cutaneous superior lip 10 (6), ear (3)	No	Yes	Yes	No	No	No	No
	radiotherapy	65.4	46	11.7 mm	nose (28), cheek, pre- and retroauricular areas (24), eyelids, internal and external eye angles (20), forehead, temple, between eyebrows (17), chin, cutaneous superior lip (7),							

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
					ear (3)							
Bath-Hextall 2014 24332516	Imiquimod	NR	41	median 12 mm	face (37), trunk (38), neck (6), arm (6), leg (10), other (3)	Yes	Yes	Yes	No	No	Yes	No
	excision	NR	40	median 10 mm	face (33), trunk (39), neck (9), arm (7), leg (9), other (3)							
Beutner 1999 10570388	imiquimod 2x/day	NR	NR	NR	upper exremity (57), anterior upper trunk (14), neck (29)	No	No	No	Unsure	Yes	unsure	Yes
	imiquimod 1x/day	NR	NR	NR	upper extremity (50), anterior upper trunk (25), posterior upper trunk (25)							
	imiquimod 2x/week	NR	NR	NR	lower extremity (20), anterior upper trunk (40), posterior upper trunk (20), neck (20)							
	imiquimod 1x/week	NR	NR	NR	lower extremity (50), anterior upper trunk (25), posterior upper trunk (25)							
	vehicle (3 2x/day, 2 1x/day, 2 3x/week, 2 2x/week, 2 1x/week)	NR	NR	NR	face (9), upper extremity (46), anterior upper trunk (9), neck (9), posterior lower trunk (27)							
Brinkhuizen 2016 27067393	Diclofenac (results superficial/nod	63.0/78.5	25	61.7/49.5 mm2	extremities (47), trunk/neck (53)	Yes	Yes	No	No	No	Yes	Yes

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
	ular)											
	Calcitriol (results superficial/nodular)	65.5/68.5	22	54.2/59.7 mm2	trunk/neck (59), genetalia (41)							
	Diclofenac + Calcitriol (results superficial/nodular)	67.5/71	37.5	46.7/44.8 mm2	trunk/neck (50), genetalia (44)							
	No treatment (results superficial/nodular)	61.5/66	37.5	59.7/53.4 mm2	extremities (53), trunk/neck (47)							
Cornell 1990 2229497	interferon	56	19	83 mm2	head and face (25), extermities (12), trunk/neck (63)	Yes	No	Yes	Yes	No	Yes	Yes
	placebo	57	14	75 mm2	head and face (17), extermities (14), trunk/neck (59)							
Edwards 1990 2107219	interferon gamma, 0.01	NR	NR	NR	NR	No	No	unsure	unsure	unsure	unsure	Yes
	interferon gamma, 0.05	NR	NR	NR	NR							
Edwards 1990 2383027	Interferon alfa-2b, 30 million IU	NR	NR	NR	NR	No	No	unsure	Yes	Yes	Yes	Yes
	Interferon alfa-2b, 10 million IU	NR	NR	NR	NR							
Eimpunth 2014	Laser vs. no treatment	NR	33	NR	NR	No Data	unsure	unsure	No	unsure	unsure	Yes
Garcia-Martin 2011	imiquimod 5%	73.1	33.3	7.6 mm	eyelid (100)	No	No	Yes	No	Unsure	Unsure	Yes

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
21242584												
	radiotherapy	74.2	41.7	7.41 mm	eyelid (100)							
Geisse 2004 15097956	Imiquimod 5x/wk	58.4	37	NR	neck (4), trunk: anterior lower (1), trunk: anterior upper (17), trunk: posterior lower (7), trunk: posterior upper (24), lower extremity (excluding foot) (15), upper extremity (excluding hand) (31), chin (1), forehead (1)	Yes	Yes	No	Yes	Yes	Yes	Yes
	Vehicle 5x/wk or 7x/wk	58.7	38	NR	neck (1), trunk: anterior lower (1), trunk: anterior upper (20), trunk: posterior lower (6), trunk: posterior upper (20), lower extremity (excluding foot) (10.5), upper extremity (excluding hand) (39), cheek (1), chin (1), forehead (1)							
	Imiquimod 7x/wk	59.4	41	NR	neck (5), trunk: anterior lower 3,							

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
					trunk: anterior upper (13), trunk: posterior lower (8), trunk: posterior upper (26), lower extremity (excluding foot) (11), upper extremity (excluding hand) (33), cheek (1), chin (1), forehead (1) Face: nose 1 (1%)							
Hall 1986 3514075	Radiotherapy	NR	NR	NR	face and neck (82), eyelid (6), trunk (12)	No	No	No	No	No	No	Unsure
	Cryotherapy	NR	NR	NR	face and neck (65), eyelid (17), trunk (17)							
Marks 2001 11312429	Imiquimod	61	27	NR	Upper extremities (32), upper trunk (28), head/neck/lower limbs (40)	No	No	unsure	No	unsure	unsure	Yes
Migden 2015 25981810	sonidegib 200	median 67	39	NR	head and neck (100)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	sonidegib 800	median 65	36	NR	head and neck (100)							
Miller 1997 8996264	5FU	61	20	80 mm2	head (7), extremities (40), trunk/neck (52)	No	No	unsure	Yes	Yes	Yes	No
Mosterd 2008	MMS	67.4	39.7	1.28 cm2	frontal/temporal (26), cheek/chin	Yes	Yes	Unsure	No	No	No	No

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
19010733					(9), (peri)nasal (34), lips/perioral (7), periocular (8), ears (4), periauricular (12)							
	Surgical excision	68.7	38.2	1.77 cm2	frontal/temporal (32), cheek/chin (8), (peri)nasal (30), lips/perioral (4), periocular (8), ears (8), periauricular (10)							
Salmanpoor 2012	Surgical excision	57.3	37	NR	face and scalp (100)	No	No	unsure	Unsure	Unsure	Unsure	Yes
	Curettage	57.3	37	NR	face and scalp (100)							
	Electodessication and curettage	57.3	37	NR	face and scalp (100)							
Thissen 2000 10940063	cryotherapy	NR	NR	NR	face (46), eyelid (4), ear (4), trunk/neck (6), forehead/temple (34), chin/perioral (6)	No	No	Yes	No	Unsure	Unsure	Yes
	surgical excision	NR	NR	NR	face (43), eyelid (8), trunk/neck (14), forehead/temple (25), chin/perioral (10)							
Torres 2004	imiquimod, 2 weeks	NR	33.3	median 0.9 cm2	NR	Yes	No	Yes	Yes	Yes	Unsure	Yes

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
15606733												
	imiquimod, 4 weeks	NR	41.7	median 0.8 cm2	NR							
	imiquimod, 6 weeks	NR	33.3	median 1.2 cm2	NR							
	vehicle controlled-pooled	NR	19.4	median 1.2 cm2	NR							
Tran 2012 22511036	S1: PDL 15 j/cm2	NR	57	88 mm2	extremities (12), trunk/neck (88)	No	No	No	Yes	No	No	Yes
	S2: PDL 7.5 j/cm2	NR	43	105 mm2	extremities (50), trunk/neck (50)							
	No treatment	NR	43	94 mm2	extremities (43), trunk/neck (57)							
Wang 2001 11298545	Total (ALA-PDT vs. Cryotherapy)	NR	50	NR	legs (11), arms (7), trunk (54), head/neck (28)	Unsure	Unsure	Unsure	No	No	Unsure	Yes

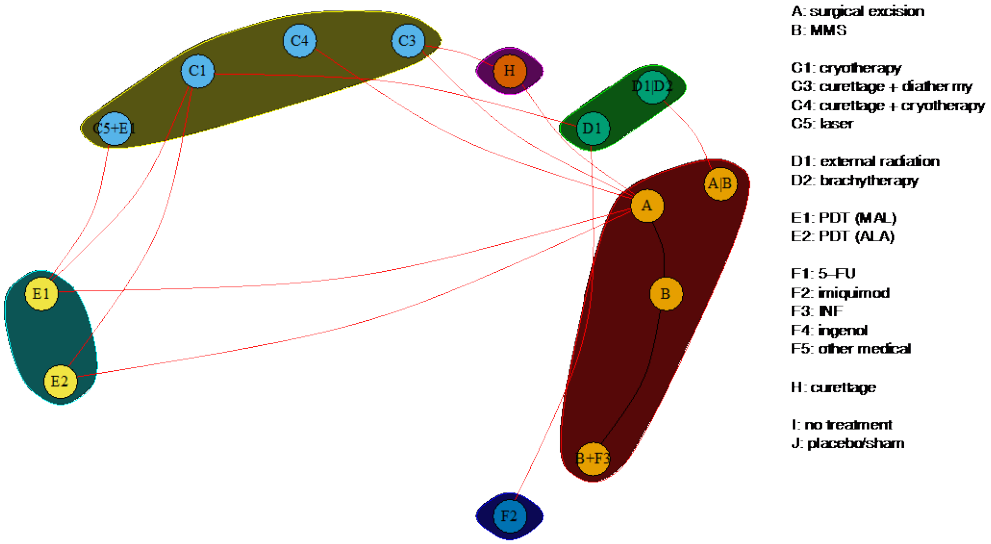
*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm. NR=not reported.

Recurrence, all BCC lesions

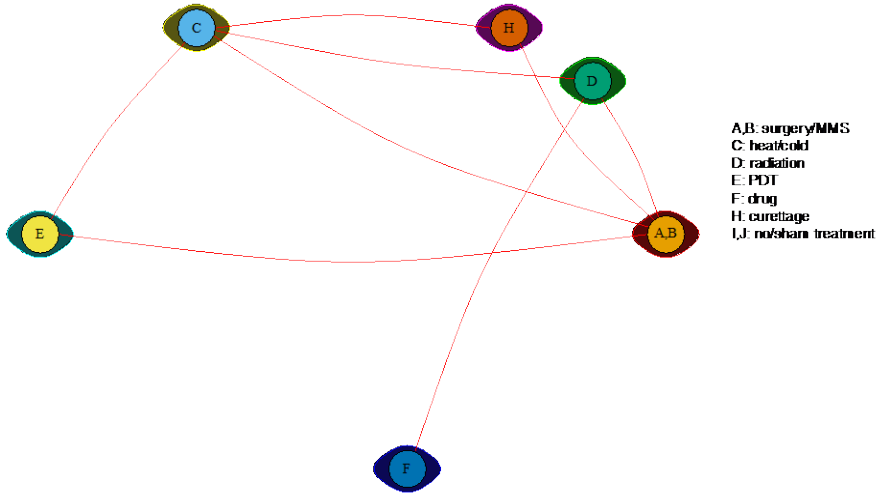
The evidence graph for recurrence with respect to individual treatments is sparse (Figure 6 [A] – reproduced in Figure 7 [A] for ease of reference), and comprises two connected subgraphs. Detailed results at the RCT-level are in the appendix.

Figure 7: Evidence graph of RCTs evaluating recurrence in BCCs across (A) individual interventions and types of interventions (B).

(A)



(B)



Note that the evidence graph for the individual treatments comprises 2 connected subgraphs defined by the following sets of nodes: A|B, D1|D2; and all remaining nodes.

Comparisons across intervention categories

In total, 11 RCTs (1234 lesions) were included in this analysis.[18, 19, 41, 46, 47, 63, 66, 67, 81, 86, 100] Eight RCTs were deemed to be at low or moderate risk of bias. Cumulative sample sizes per comparison ranged from 27 to 347; for more details see the box below:

Studies (total sample)	11 (1234)
Total sample by intervention	(A,B): 403; (E): 307; (D): 234; (F): 15; (C): 255; (H): 20
Total sample by intervention, (min, max)	15, 403
Data by comparison	(A,B--E): 3 (305); (A,B--D): 1 (347); (A,B--C): 2 (134); (A,B--H): 1 (44); (E--C): 3 (308); (D--F): 1 (27); (D--C): 1 (93); (C--H): 1 (45)
Studies by comparison (min, max)	1, 3
Total sample by comparison (min, max)	27, 347
Followup median (min, max)	28 (12, 96) months

Table 7 shows the relative odds ratios for recurrence across intervention categories. Overall, surgical treatments (A,B), radiation (D), and drugs (F), appear to be better than interventions that destroy lesions with heat or cold (C), photodynamic therapies (E), or curettage (H); and in many instances in the Table, statistically significantly so. There are no statistically significant differences among the intervention categories in the former set (namely, [A,B], D, F) or among those in the latter set (namely, C, E, H), but almost universally, the confidence intervals are broad and cannot exclude large differences in the odds of recurrence in either direction.

In the Table, shaded cells correspond comparisons that have been inferred from the analysis model but have not been examined in the included RCTs. For example, comparisons of drugs (F) versus other intervention categories are mostly indirect, and drugs have been compared head-to-head only with radiation (D). Indirect comparisons are more uncertain than those for which head-to-head data exist. The added uncertainty in indirect comparisons is partly reflected in the width of the respective 95 percent confidence intervals, which is (often much) broader for comparisons without direct data. For all comparisons that are empirically observed (all non-shaded cells in the Table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 7 (see Appendix I).

Table 7. Relative odds ratios for recurrence between intervention categories (all BCC lesions)

Surgery/MMS (A,B)	0.13 (0.05, 0.35)	0.77 (0.22, 2.73)	0.12 (0.04, 0.32)	1.09 (0.05, 24.23)	0.14 (0.03, 0.77)
7.71 (2.83, 20.98)	Heat/cold (C)	5.95 (2.03, 17.4)	0.91 (0.43, 1.95)	8.44 (0.41, 173.75)	1.09 (0.23, 5.16)
1.3 (0.37, 4.59)	0.17 (0.06, 0.49)	Radiation (D)	0.15 (0.05, 0.45)	1.42 (0.06, 32.2)	0.18 (0.03, 1.04)
8.45 (3.08, 23.16)	1.1 (0.51, 2.34)	6.52 (2.21, 19.21)	PDT (F)	9.25 (0.45, 190.91)	1.19 (0.25, 5.68)
0.91 (0.04, 20.24)	0.12 (0.01, 2.44)	0.7 (0.03, 15.99)	0.11 (0.01, 2.23)	Drugs (F)	0.13 (<0.005, 3.56)
7.08 (1.3, 38.49)	0.92 (0.19, 4.35)	5.46 (0.96, 31.02)	0.84 (0.18, 3.99)	7.75 (0.28, 214.11)	Curettage (H)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 8 offers complementary information from the same analysis; for each intervention category, it shows the mean recurrence rate across the included RCTs. Surgical treatments,

radiation, and drugs RCT arms had on average lower recurrence rates (3.1% to 4.4%) compared to photodynamic therapy, curettage, and interventions that destroy lesions with heat or cold, which had average recurrence in the 20 to 23 percent range.

Table 8. Mean and forecasted recurrence rates by intervention category (all BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
Surgery/MMS (A,B)	3.4 (1.5, 7.6)	3.4 (1.0, 11.4)
Heat/cold (C)	21.4 (13.8, 31.6)	21.4 (8.3, 45.1)
Radiation (D)	4.4 (1.8, 10.4)	4.4 (1.2, 15.0)
PDT (E)	23.0 (14.8, 33.9)	23.0 (8.9, 47.5)
Drugs (F)	3.1 (0.2, 38.8)	3.1 (0.1, 42.5)
Curettage (H)	20.0 (5.5, 51.9)	20.0 (4.1, 59.1)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Comparisons across individual interventions

The results of the analyses of intervention categories are congruent with the corresponding results of the analyses of individual interventions. As evident from Figure 7, there are two connected subgraphs: a smaller one comprising the comparison between surgical treatments (surgical excision or MMS, [A,B]]) and external radiation of brachytherapy (D1|D2), and a larger one with all other interventions. In total, 13 RCTs (1389 lesions) were included in this analysis.[18, 19, 41, 46, 47, 63, 66, 67, 77, 81, 86, 100, 101] They are described in the box below.

	First subgraph[18, 19, 41, 47, 63, 66, 67, 77, 81, 86, 100, 101]	Second Subgraph[46]
Studies (total sample)	12 (1042)	1 (347)
Total sample by intervention	(A): 298; (E2): 127; (D1): 61; (F2): 15; (C1): 176; (C4): 38; (C3): 25; (H): 20; (B): 77; (E1): 180; (B+F3): 9; (C5+E1): 16	(A|B): 174; (D1|D2): 173
Total sample by intervention, (min, max)	9, 298	173, 174
Data by comparison	(A--E2): 1 (171); (A--C4): 1 (85); (A--C3): 1 (49); (A--H): 1 (44); (A--B): 1 (140); (A--E1): 2 (134); (E2--C1): 1 (83); (D1--F2): 1 (27); (D1--C1): 1 (93); (C1--E1): 1 (193); (C3--H): 1 (45); (B--B+F3): 1 (15); (E1--C5+E1): 1 (32)	(A|B--D1|D2): 1 (347)
Studies by comparison (min, max)	1, 2	1, 1
Total sample by comparison (min, max)	15, 193	347, 347
Followup median (min, max)	28 (12, >120) months	41 (41, 41) months

A: surgical excision, B: Mohs Micrographic Surgery; C1: cryotherapy; C3: diathermy and curettage; C4: cryotherapy and curettage; D1: external radiation; E1: MAL photodynamic therapy; E2: ALA photodynamic therapy; F2: Imiquimod; H: curettage.

Tables 9 and 10 show the relative effects for the larger and smaller subgraphs, respectively. Because the comparisons across individual interventions are sparse, however, the confidence

intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the compared interventions.

Table 11 shows, for each intervention, the mean recurrence rates across all RCTs; estimates for interventions in both subgraphs are listed in the Table. One cannot compare statistically the estimated recurrence rates between an intervention in the first subgraph (e.g., cryotherapy [C1]) and the second subgraph (e.g., external radiation or brachytherapy [D1|D2]), because they come from disjoint analyses. The mean recurrence rates for individual interventions follow the same pattern as the corresponding recurrence rates for intervention categories. For example, the point estimates for the mean recurrence rate for surgical excision (A), MMS (B), and a combination of MMS and interferon (B+F3) ranged between 4.0 and 4.6 percent; and it was estimated at 3.4 percent for surgical interventions (A,B) in Table 8.

Table 9. Relative odds ratios for recurrence between individual interventions (all BCC lesions, first subgraph).

Surgical excision (A)	1.08 (0.22, 5.35)	0.95 (0.04, 22.91)	0.15 (0.05, 0.46)	0.7 (0.12, 4.24)	0.22 (0.07, 0.71)	0.37 (0.06, 2.14)	1.77 (0.33, 9.39)	0.16 (0.05, 0.49)	0.09 (0.03, 0.28)	1.51 (0.06, 35.99)	0.24 (0.05, 1.13)
0.92 (0.19, 4.55)	MMS (B)	0.87 (0.03, 24.17)	0.14 (0.03, 0.75)	0.65 (0.07, 6.33)	0.21 (0.03, 1.33)	0.34 (0.04, 2.94)	1.63 (0.2, 13.11)	0.15 (0.03, 0.79)	0.08 (0.01, 0.45)	1.39 (0.05, 41.89)	0.22 (0.03, 1.8)
1.15 (0.04, 31.79)	1.15 (0.04, 31.79)	MMS+INF (B+F3)	0.16 (0.01, 3.81)	0.74 (0.02, 25.66)	0.24 (0.01, 6.43)	0.39 (0.01, 12.14)	1.87 (0.06, 55.76)	0.17 (0.01, 4.01)	0.09 (<0.005, 2.24)	1.59 (0.02, 121.29)	0.26 (0.01, 7.86)
6.49 (2.19, 19.18)	7.04 (1.34, 36.89)	6.14 (0.26, 143.35)	Cryotherapy (C1)	4.55 (0.69, 30.05)	1.46 (0.37, 5.77)	2.38 (0.49, 11.49)	11.48 (2.88, 45.74)	1.05 (0.56, 1.95)	0.57 (0.24, 1.36)	9.77 (0.44, 218.9)	1.58 (0.31, 8.13)
1.43 (0.24, 8.63)	1.55 (0.16, 15.15)	1.35 (0.04, 46.72)	0.22 (0.03, 1.45)	Diathermy+ curettage (C3)	0.32 (0.04, 2.49)	0.52 (0.05, 5.45)	2.53 (0.26, 24.51)	0.23 (0.03, 1.54)	0.13 (0.02, 0.87)	2.15 (0.06, 73.02)	0.35 (0.06, 2.13)
4.46 (1.42, 14.02)	4.83 (0.75, 30.98)	4.21 (0.16, 114.2)	0.69 (0.17, 2.72)	3.12 (0.4, 24.24)	Cryotherapy + curettage (C4)	1.64 (0.23, 11.55)	7.89 (1.22, 51.16)	0.72 (0.18, 2.89)	0.39 (0.09, 1.65)	6.71 (0.25, 178.59)	1.09 (0.18, 6.7)
2.72 (0.47, 15.85)	2.95 (0.34, 25.58)	2.57 (0.08, 80.37)	0.42 (0.09, 2.02)	1.91 (0.18, 19.84)	0.61 (0.09, 4.31)	Laser+ PDT (MAL) (C5+E1)	4.82 (0.62, 37.3)	0.44 (0.1, 1.97)	0.24 (0.04, 1.31)	4.1 (0.14, 124.25)	0.66 (0.08, 5.66)
0.57 (0.11, 3)	0.61 (0.08, 4.92)	0.53 (0.02, 15.92)	0.09 (0.02, 0.35)	0.4 (0.04, 3.84)	0.13 (0.02, 0.82)	0.21 (0.03, 1.61)	External radiation (D1)	0.09 (0.02, 0.4)	0.05 (0.01, 0.24)	0.85 (0.03, 22.34)	0.14 (0.02, 1.09)
6.21 (2.06, 18.7)	6.73 (1.26, 35.8)	5.87 (0.25, 138.24)	0.96 (0.51, 1.78)	4.35 (0.65, 29.1)	1.39 (0.35, 5.61)	2.28 (0.51, 10.23)	10.98 (2.51, 48.11)	PDT (MAL) (E1)	0.54 (0.21, 1.44)	9.35 (0.41, 212.36)	1.51 (0.29, 7.89)
11.4 (3.6, 36.08)	12.36 (2.23, 68.68)	10.78 (0.45, 260.53)	1.76 (0.74, 4.19)	7.99 (1.15, 55.48)	2.56 (0.61, 10.79)	4.19 (0.76, 23.01)	20.18 (4.18, 97.47)	1.84 (0.69, 4.86)	PDT (ALA) (E2)	17.17 (0.73, 401.94)	2.78 (0.51, 15.11)
0.66 (0.03, 15.87)	0.72 (0.02, 21.72)	0.63 (0.01, 47.82)	0.1 (<0.005, 2.29)	0.47 (0.01, 15.81)	0.15 (0.01, 3.97)	0.24 (0.01, 7.4)	1.18 (0.04, 30.85)	0.11 (<0.005, 2.43)	0.06 (<0.005, 1.36)	Imiquimod (F2)	0.16 (0.01, 4.84)
4.1 (0.88, 19.02)	4.45 (0.56, 35.54)	3.88 (0.13, 118.24)	0.63 (0.12, 3.25)	2.87 (0.47, 17.63)	0.92 (0.15, 5.68)	1.51 (0.18, 12.87)	7.26 (0.92, 57.44)	0.66 (0.13, 3.45)	0.36 (0.07, 1.96)	6.18 (0.21, 184.67)	Curettage (H)

Table 10. Relative odds ratios for recurrence between individual interventions (all BCC lesions, second subgraph).

Surgical excision /MMS (A|B)	0.12 (0.01, 0.96)
8.39 (1.04, 67.8)	External radiation/ brachytherapy (D1|D2)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 11. Mean recurrence rates by intervention category (all BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
First subgraph:		
Surgical excision (A)	4.3 (1.8, 9.8)	4.3 (1.0, 17.3)
MMS (B)	4.0 (0.9, 16.0)	4.0 (0.6, 23.0)
MMS+INF (B+F3)	4.6 (0.2, 50.9)	4.6 (0.2, 57.0)
Cryotherapy (C1)	22.6 (12.9, 36.6)	22.6 (6.6, 55.0)
Diathermy+curettage (C3)	6.0 (1.1, 27.4)	6.0 (0.7, 36.0)
Cryotherapy+curettage (C4)	16.7 (5.6, 40.3)	16.7 (3.4, 53.5)
Laser+PDT (MAL) (C5+E1)	10.9 (2.6, 36.4)	10.9 (1.7, 47.3)
External radiation (D1)	2.5 (0.6, 9.6)	2.5 (0.4, 14.6)
PDT (MAL) (E1)	21.9 (12.0, 36.5)	21.9 (6.2, 54.3)
PDT (ALA) (E2)	34.0 (18.4, 54.0)	34.0 (10.3, 69.8)
Imiquimod (F2)	2.9 (0.1, 38.7)	2.9 (0.1, 44.8)
Curettage (H)	15.6 (4.0, 45.3)	15.6 (2.6, 56.6)
Second subgraph		
Surgical excision or Mohs (A|B)	0.6 (0.1, 4.0)	NA
External radiation or brachytherapy (D1|D2)	4.6 (2.3, 9.0)	NA

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy; INF=interferon

Recurrence, subgroup analyses by lesion type

We conducted subgroup analyses by the type of BCC lesion. We report analyses comparing intervention categories, but not analyses comparing individual treatments. The latter are very sparse, and their results are very similar to the pertinent comparisons in Tables 9 and 10.

Many subgroup analyses per lesion type are possible; we describe here analyses in RCTs of lower-risk lesions (strata of predominantly [>80%] superficial BCCs, predominantly nodular BCCs, and superficial or nodular BCCs) overall, and broken down by lesion type; and of higher-risk lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).

Eleven RCTs (n=1234 lesions) included low risk BCCs (nodular and superficial subtypes). All results about comparisons among intervention categories are the same as in the previous section (Tables 7 and 8).

With respect to RCT strata of predominantly superficial lesions, a single RCT deemed to be at low risk of bias compared cryotherapy (C1, n=93) with PDT with MAL (E1, n=100).[47] Its results are shown in Tables 12 and 13 for a followup of 60 months. Briefly, there was no statistically significant difference between the two interventions, but based on the width of the 95% confidence interval one cannot exclude differences in the odds of the outcome as large as 80% in either direction.

Table 12. Relative odds ratios for recurrence between interventions (predominantly superficial BCC lesions)

Heat/cold (C) [Cryotherapy (C1)]	0.91 (0.46, 1.82)
1.10 (0.55, 2.19)	PDT (E) [PDT (MAL) (E1)]

Table 13. Mean recurrence rates by intervention category (predominantly superficial BCC lesions).

Intervention type	Mean recurrence rate (95% CI)
Heat/cold (C) [Cryotherapy (C1)]	20.4 (13.4, 29.8)
PDT (E) [PDT (MAL) (E1)]	22.0 (14.9, 31.2)

Forecasted expected recurrence rates in groups of patients similar to the patients included in the analyzed RCTs are not given, because these results are from a fixed effects analysis.

The corresponding results for predominantly nodular lesions are listed in Tables 14 and 15. These results are congruent with the corresponding results from the analyses in Tables 7 and 8. The tables include information on two connected subgraphs, described in the box below.

	First subgraph[19, 41, 66, 81]	Second Subgraph[63]
Studies (total sample)	4 (337)	1 (27)
Total sample by intervention	(A,B): 158; (E): 163; (C): 16	(D): 12; (F): 15
Total sample by intervention, (min, max)	16, 163	12, 15
Data by comparison	(A,B--E): 3 (305); (E--C): 1 (32)	(D--F): 1 (27)
Studies by comparison	1, 3	1, 1

(min, max)		
Total sample by comparison (min, max)	32, 305	27, 27
Followup median (min, max)	48 (12, 96)	24 (24, 24) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs.

Table 14. Relative odds ratios for recurrence between interventions (predominantly nodular BCC lesions)

Surgery/MMS (A,B)	0.04 (<0.005, 1.08)	0.05 (<0.005, 0.53)		
22.24 (0.92, 535.74)	Heat/cold (C)	1.09 (0.07, 17.33)		
20.31 (1.88, 219.33)	0.91 (0.06, 14.45)	PDT (E)		
			Radiation (D)	1.24 (0.02, 67.04)
			0.81 (0.01, 43.6)	Drugs (F)

Results from comparisons in the first and second subgraphs are shown in the upper left and lower right blocks in this Table.

Table 15. Mean and forecasted recurrence rates by intervention category (predominantly nodular BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
First subgraph		
Surgery/MMS (A,B)	1.0 (0.1, 7.3)	1.0 (0.1, 16.2)
Heat/cold (C)	18.7 (1.9, 73.0)	18.7 (0.9, 85.5)
PDT (E)	17.4 (5.7, 42.6)	17.4 (1.8, 71.2)
Second subgraph		
Radiation (D)	3.8 (0.2, 40.3)	NA
Drugs (F)	3.1 (0.2, 35.0)	NA

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy; INF=interferon

Finally, with respect to high risk lesions, a single RCT compared surgical excision (A) with MMS (B) in histologically aggressive facial lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).[77] Although the average recurrence rate was smaller in the MMS arm (3.4% [95% CI 1.0% to 11.0%]) versus the surgical excision arm (4.8% [95% CI, 2.5% to 8.8%]), it was not significantly so (odds ratio for surgical excision versus MMS 1.43 [95% CI 0.35 to 5.95]).

Recurrence, other subgroup analyses (lesion location, lesion size)

Table 16 summarizes results from two RCTs by lesion location and size. One RCT comparing surgical excision (A) versus MAL PDT (E) in predominantly nodular lesions[21, 81] examined subgroups defined by lesion diameter (<=10 mm versus 10 to 20 mm) and found no evidence of effect modification by lesion size at one through 5 years of follow up. Another RCT comparing cryotherapy (C) to radiation therapy (D) in low-risk lesions (mixed superficial and nodular BCCs) found no

evidence of effect modification by lesion size (smaller than 10 mm, between 10 and 20 mm, and larger than 20 mm) or location (eyelids, face or neck, and trunk).[67]

Table 16. Subgroup results by lesion size and location for recurrence in (BCC lesions)

Study	Comparison	Timepoint	Subgroup	n/N arm 1 vs. n/N arm 2	OR (95% CI); P-Value Within	P- Value Between
Rhodes 2004 14732655	Excision (A) vs MAL-PDT (E)	12 months	lesion diameter: 10-20 mm	0/14 vs. 1/19	0.43 (0.02, 11.23); p=1.00	NA
			lesion diameter: <= 10 mm	0/34 vs 1/29	0.28 (0.01, 7.02); p=0.46	
		24 months	lesion diameter: 10-20 mm	0/14 vs. 0/19	NA	NA
			lesion diameter: <= 10 mm	0/29 vs. 3/29	0.13 (0.01, 2.60); p=0.24	
		36 months	lesion diameter: 10-20 mm	1/14 vs. 1/19	1.38 (0.08, 24.23); p=1.00	NA
			lesion diameter: <= 10 mm	0/29 vs. 1/29	0.32 (0.01, 8.24); p=1.00	
		48 months	lesion diameter: 10-20 mm	1/14 vs. 0/19	4.33 (0.16, 114.58); p=0.42	NA
			lesion diameter: <= 10 mm	0/29 vs. 0/29	NA	
		60 months	lesion diameter: 10-20 mm	0/14 vs 0/19	NA	NA
			lesion diameter: <= 10 mm	0/29 vs 0/29	NA	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D) therapy	12 months	Lesion location: eyelids	3/6 vs. 0/3	7.00 (0.25, 192.26); p=0.464	p= 0.97
			Lesion location: face/neck	12/30 vs. 2/40	12.67 (2.56, 62.65); p<0.001	
			Lesion location: trunk	2/8 vs. 0/6	5.00 (0.20, 125.78); p=0.473	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D) therapy	12 months	Lesion diameter <10 mm	6/19 vs. 0/19	18.78 (0.97, 362.00); p=0.020	NA
			Lesion diameter 10-20 mm	9/23 vs. 2/25	7.39 (1.39, 39.27); p=0.016	
			Lesion diameter >20 mm	2/2 vs. 0/5	55.00 (0.83, 3650.69); p=0.048	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D) therapy	24 months	Lesion location: eyelids	3/6 vs. 0/3	7.00 (0.25, 192.26); p=0.464	NA
			Lesion location: face/neck	12/30 vs. 2/40	12.67 (2.56, 62.65); p<0.001	
			Lesion location: trunk	2/8 vs. 0/6	5.00 (0.20, 125.78); p=0.473	
Hall 1986 3514075	Cryotherapy (E) vs Radiation (D) therapy	12 months	Lesion diameter <10 mm	6/19 vs. 0/19	18.78 (0.97, 362.00) p=0.020	NA
			Lesion diameter 10-20 mm	9/23 vs. 2/25	7.39 (1.39, 39.27); p=0.016	
			Lesion diameter >20 mm	2/2 vs. 0/5	55.00 (0.83, 3650.69); p=0.048	

NA = not significant; PDT = photodynamic therapy

Recurrence, results from non-randomized studies (BCC lesions)

Two NRCSs reported on recurrence in populations with only BCC lesions. The first included 74 patients and reported on a matched population of 94 superficial (64%) and nodular (36%) BCCs 25 months after treatment. The study was rated as having a moderate risk of confounding bias because of lack of blinding, and unclear reporting. The mean age at baseline was 66 (range: 49 to 90), 47 percent of the population was female. Recurrence was similar across groups (4.2% in the ALA-PDT group vs. 43% in the surgical excision group; OR: 0.96 [95% CI 0.13 to 7.09]).[144] The second reported recurrence in 621 people (47% female) with BCC lesions (38.5% superficial, 17% nodular, and 44.5% infiltrative, micronodular, morpheaform, or sclerosing). This study was judged to have a high risk of confounding and selection bias because of lack of blinding, unclear distribution of dropouts, unclear results reporting, and uneven groups at baseline that were not accounted for in the analysis. Surgical excision had a higher rate of recurrence up to 5 years compared to Imiquimod (HR 2.13; 95% CI 1.28 to 3.53).[145]

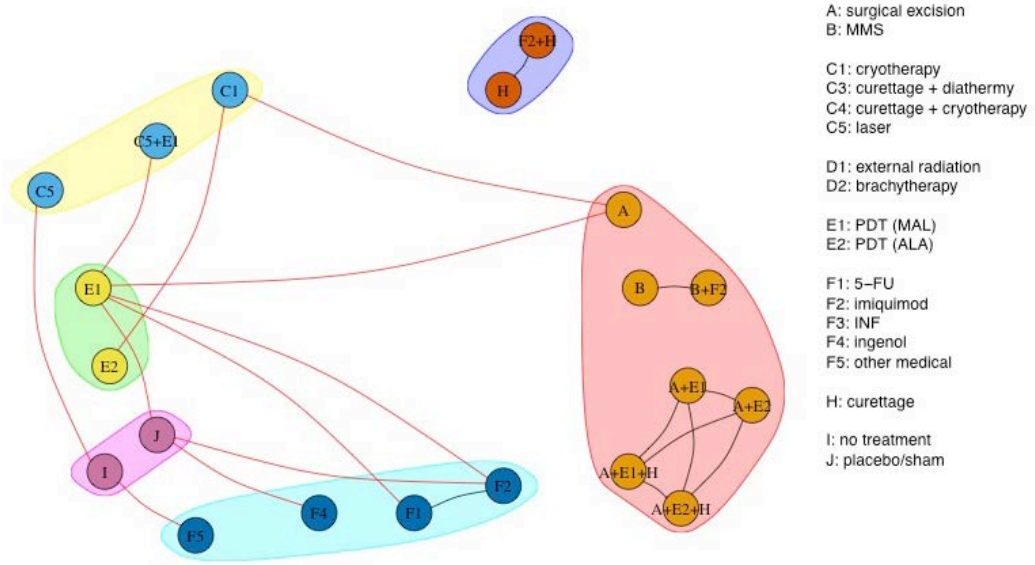
Two NRCS reported on recurrence in populations with both BCCs and SCC lesions. One reported on 1174 patients with 1488 lesions in a Veterans Affairs clinic. This study was deemed to have a low risk of bias, with balanced groups, consecutive recruitment, blinding of outcome assessors, and adequate accounting for people lost to followup. Most (75%) of the lesions were BCCs; the other 25 percent were SCCs; 26 percent were female, 40 percent had a Fitzpatrick skin score of I or II, and 3 percent were immunocompromised due to prior solid-organ transplant. The lesions were treated by Mohs surgery (246; 65% in the H-zone of the face), surgical excision (251; 26% in H-zone of the face), and electrodessication and curettage (ED&C) (136; 11% in H-zone of the face). ED&C had the highest rate of recurrence after 5 years (4.9%), then excision (3.5%), and finally Mohs (2.1%). In a subsample of 240 pairs of tumors matched on propensity score, Mohs had a lower adjusted rate of recurrence than excision (HR 0.65; 95% CI 0.33, 1.27)[138, 140-143] The second NRCS reported on two doses and schedules of orthovoltage radiotherapy. The population consisted of 436 lesions in 385 elderly people, with BCCs (71%) and SCCs (29%). The mean age was 78, and 42 percent were female. A lower dose of radiation (3675 cGy) had a non-significantly higher recurrence rate than the higher dose (4500 cGy) (HR: 0.483; 95% CI 0.065 to 3.58).[147]

Lack of histologic clearance (all BCC lesions)

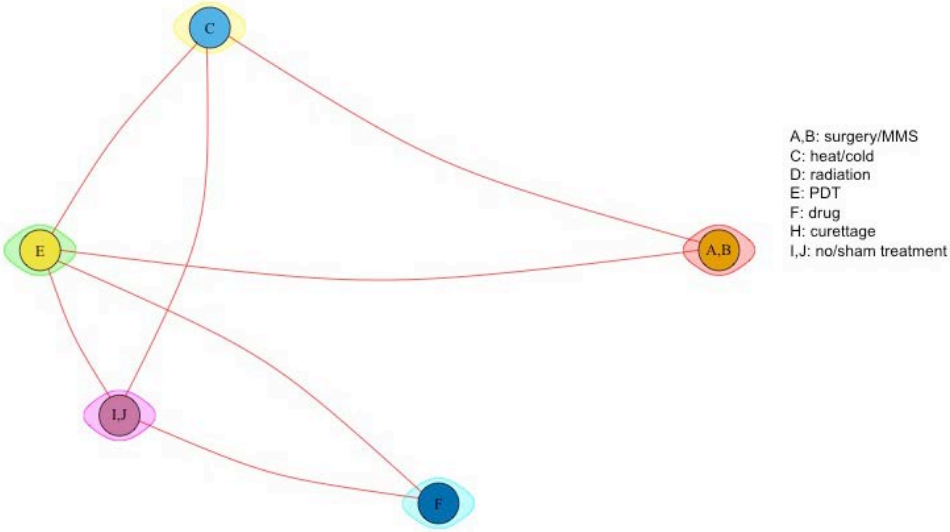
The evidence graph for lack of histologic clearance with respect to individual treatments is sparse (Figure 6 [B] – reproduced in Figure 8 [A] for ease of reference) and comprises 5 connected subgraphs. Detailed results at the RCT-level are in the appendix.

Figure 8. Evidence graph of RCTs evaluating lack of histological clearance in BCCs across (A) individual interventions and types of interventions (B).

(A)



(B)



Note that the evidence graph for the individual treatments comprises 5 connected subgraphs defined by the following sets of nodes: H, F2+H; B, B+F2; C5, F5, I; A+E1, A+E1+H, A+E2, A+E2+H; and the set of all remaining nodes.

Comparisons across intervention categories

In total, 15 RCTs (1940 lesions) were included in this analysis.[41, 45, 50, 51, 60, 62, 64-66, 88-90, 95, 97, 100] Twelve RCTs were deemed to be at low or moderate risk of bias. Cumulative sample sizes per comparison ranged from 44 to 1196; for more details see the box below.

Studies (total sample)	15 (1940)
Total sample by intervention	(F): 825; (I,J): 607; (A,B): 83; (C): 131; (E): 294
Total sample by intervention, (min, max)	83, 825
Data by comparison	(F--I,J): 7 (1196); (F--E): 1 (271); (I,J--C): 2 (44); (I,J--E): 1 (150); (A,B--C): 1 (96); (A,B--E): 1 (68); (C--E): 2 (115)
Studies by comparison (min, max)	1, 7
Total sample by comparison (min, max)	44, 1196
Followup median (min, max)	3 (1.5, 36) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Table 17 shows the relative odds ratios for lack of histologic clearance across intervention categories. Overall, surgical treatments (A,B) were statistically significantly better than any other intervention category in terms of histological clearance. No or sham treatment (I,J) was statistically significantly worse that all other treatments. Among the other intervention categories, the odds ratios favor PDT (E) over interventions that destroy lesions with heat or cold (C), and the latter (C) over drugs (F), but these differences are not statistically significant. Further, the confidence intervals for the comparisons between the latter three treatments are broad and cannot exclude large effects in either direction.

In the Table, shaded cells correspond to comparisons that have been inferred from the analysis model, but that have not been examined in the included RCTs. For example, comparisons of surgical treatments (A,B) or interventions that destroy lesions with heat or cold (C) versus drugs (F) or placebo (I,J) are indirect, through PDT (E) as the common comparator. Indirect comparisons are more uncertain that those for which head-to-head data exist. The added uncertainty in the indirect comparisons is partly reflected in the width of the respective 95 percent confidence intervals, which is (often much) broader for comparisons without versus with direct data. For all comparisons that have been empirically observed (all non-shaded cells in the Table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 17 (see Appendix I).

Table 17. Relative odds ratios for lack of histologic clearance between intervention categories (all BCC lesions)

Surgery/MMS (A,B)	0.04 (<0.005, 0.77)	0.05 (<0.005, 1.03)	0.02 (<0.005, 0.41)	<0.005 (<0.005, 0.04)
27.5 (1.3, 579.51)	Heat/cold (C)	1.36 (0.22, 8.45)	0.6 (0.11, 3.16)	0.07 (0.01, 0.34)
20.11 (0.97, 418.64)	0.73 (0.12, 4.54)	PDT (E)	0.44 (0.09, 2.25)	0.05 (0.01, 0.24)
45.91 (2.42, 870.68)	1.67 (0.32, 8.83)	2.28 (0.44, 11.74)	Drugs (F)	0.11 (0.03, 0.45)
418.6 (22.48, 7793.78)	15.25 (2.98, 77.94)	20.81 (4.18, 103.57)	9.12 (2.2, 37.76)	No/sham treatment (I,J)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 18 offers complementary information from the same analysis. For each intervention catgory, it shows the mean fraction of lesions without histologic clearance across the included RCTs. It also forecasts the expected fractions with lack of histologic clearance in each intervention category in groups of patients similar to the patients included in the analyzed RCTs. The average number of lesions with no histological clearance was 1.2 percent in the surgery arms, between 19.5 and 35.6 percent in other active intervention categories, and 83.5 percent for no or sham (placebo) treatment.

Table 18. Mean and forecasted lack of histologic clearance fractions by intervention category (all BCC lesions).

Intervention type	Mean lack of histological clearance fraction percent (95% CI)	Forecasted lack of histological clearance fraction percent (95% CI)
Surgery/MMS (A,B)	1.2 (0.1, 15.9)	1.2 (<0.5, 36.7)
Heat/cold (C)	24.9 (8.2, 55.0)	24.9 (1.6, 87.1)
PDT (E)	19.5 (6.4, 46.4)	19.5 (1.2, 83.0)
Drugs (F)	35.6 (16.5, 60.8)	35.6 (2.9, 91.0)
No/sham treatment (I,J)	83.5 (65.5, 93.1)	83.5 (21.8, 98.9)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Comparisons across individual interventions

The results of the analyses of analyses of individual interventions are congruent with the analyses intervention categories are congruent with the corresponding results. As is evident from Figure 8, there are five connected subgraphs. Separate analyses are conducted for each connected subgraph. In total, 19 RCTs (2170 lesions) were included in these analyses, as summarized in the box:

	First subgraph[41, 45, 50, 62, 64-66, 88-90, 95, 100]	Second subgraph[69]	Third subgraph[51, 60, 97]	Fourth subgraph[92]	Fifth subgraph[52, 96]
Studies (total sample)	12 (2010)	1 (43)	3 (76)	1 (20)	2 (97)
Total sample by intervention	(F2): 761; (J): 575; (A): 83; (C1): 87; (E2): 44; (E1): 250; (F1): 146; (F4): 48; (C5+E1): 16	(A+E1): 11; (A+E1+H): 10; (A+E2): 11; (A+E2+H): 11	(C5): 28; (I): 32; (F5): 16	(F2+H): 10; (H): 10	(B): 50; (B+F2): 47
Total sample by intervention, (min, max)	16, 761	10, 11	16, 32	10, 10	47, 50
Data by comparison	(F2--J): 5 (1110); (F2--E1): 1 (271); (F2--F1): 1 (291); (J--E1): 1 (150); (J--F4): 1 (54); (A--C1): 1 (96); (A--E1): 1 (68); (C1--E2): 1 (83); (E1--F1): 1 (272); (E1--C5+E1): 1 (32)	(A+E1--A+E1+H): 1 (21); (A+E1--A+E2): 1 (22); (A+E1--A+E2+H): 1 (22); (A+E1+H--A+E2): 1 (21); (A+E1+H--A+E2+H): 1 (21); (A+E2--A+E2+H): 1 (22)	(C5--I): 2 (44); (I--F5): 1 (32)	(F2+H--H): 1 (20)	(B--B+F2): 2 (97)
Studies by	1, 5	1, 1	1, 2	1, 1	2, 2

comparison (min, max)					
Total sample by comparison (min, max)	32, 1110	21, 22	32, 44	20, 20	97, 97
Followup median (min, max)	3 (3, 36) months	2.5 (2.5, 2.5) months	2 (1.5, 2) months	2 (2, 2) months	1.5 (0.5, 2.5) months

A: surgical excision, B: Mohs Micrographic Surgery; C1: cryotherapy; C3: diathermy and curettage; C4: cryotherapy and curettage; C5: laser; D1: external radiation; E1: MAL photodynamic therapy; E2: ALA photodynamic therapy; F1: 5-FU; F2: Imiquimod; F4: Ingenol; H: curettage; J placebo.

Table 19 has results on the relative effects for the largest subgraph. Table 20 has the corresponding results for the other subgraphs: the one for the comparison of surgical excision with PDT with MAL or ALA, with or without curettage (A+E1 versus A+E2 versus, A+E1+H versus A+E2+H); and the one for the comparison between laser ablation (C5) versus diclofenac and/or calcitriol (other medication – F5) and versus no treatment (I). Table 21 shows the relative effects for the last two subgraphs, namely the one for the comparison between curettage alone (H) versus curettage and imiquimod (H+F2); and the one for the comparison between MMS (B) and MMS with imiquimod (B+F2). In all three tables, comparisons across individual observations are sparse. The confidence intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the compared interventions. The exception is for comparisons between surgical treatments and no intervention, which are statistically significant despite the wide confidence interval, because the relative effect is very large.

Table 22 shows, for each intervention, the mean fractions for lack of histologic clearance across all RCTs. Estimates for interventions in all five subgraphs are listed in the Table. One should not compare statistically these fractions across the subgraphs, because they come from disjoint analyses. In general, the mean fractions for lack of histologic clearance for individual interventions are in congruence with the corresponding fractions estimated for intervention categories. For example, in the first subgraph, the average recurrence rates for PDT with MAL (E1) and ALA (E2) were 18.2 percent (95% CI 5.1 to 48.0) and 25.0 percent (95% CI 2.0 to 84.0), respectively, and the corresponding result from the analysis between intervention categories was 19.5 percent (95% CI 6.4 to 46.4). The mean number of lesions with no histological clearance for the three medical interventions, namely 5-FU (F1), imiquimod (F2), and ingenol (F4), ranged between 5.5 and 77.1 percent, but the respective confidence intervals were very wide, and the corresponding odds ratios in Table 19 were not statistically significant.

Table 19. Relative odds ratios for lack of histological clearance between individual interventions (all BCC lesions, largest subgraph).

(A) surgery	0.11 (<0.005, 3.3)	0.02 (<0.005, 1.08)	0.05 (<0.005, 1.19)	0.04 (<0.005, 1.81)	0.21 (<0.005, 10.47)	0.04 (<0.005, 0.83)	<0.005 (<0.005, 0.18)	<0.005 (<0.005, 0.05)
9.31 (0.3, 285.72)	(C1) cryotherapy	0.19 (0.01, 6.43)	0.5 (0.04, 6.05)	0.34 (0.01, 10.68)	1.93 (0.06, 61.81)	0.39 (0.04, 4.11)	0.03 (<0.005, 1.06)	0.02 (<0.005, 0.23)
49.8 (0.93, 2678.92)	5.35 (0.16, 184.09)	(C5+E1) laser + PDT (MAL)	2.69 (0.11, 67.1)	1.8 (0.03, 99.7)	10.35 (0.19, 576.29)	2.1 (0.09, 47.08)	0.18 (<0.005, 9.86)	0.12 (0.01, 2.66)
18.52 (0.84, 407.72)	1.99 (0.17, 23.98)	0.37 (0.01, 9.28)	(E1) PDT (MAL)	0.67 (0.03, 15.3)	3.85 (0.17, 88.57)	0.78 (0.13, 4.86)	0.07 (<0.005, 1.51)	0.04 (0.01, 0.27)
27.67 (0.55, 1386.65)	2.97 (0.09, 94.42)	0.56 (0.01, 30.77)	1.49 (0.07, 34.14)	(E2) PDT (ALA)	5.75 (0.11, 298.48)	1.17 (0.06, 23.88)	0.1 (<0.005, 5.11)	0.07 (<0.005, 1.35)
4.81 (0.1, 242.47)	0.52 (0.02, 16.52)	0.1 (<0.005, 5.38)	0.26 (0.01, 5.98)	0.17 (<0.005, 9.03)	(F1) 5-FU	0.2 (0.01, 4.18)	0.02 (<0.005, 0.89)	0.01 (<0.005, 0.24)
23.66 (1.2, 464.54)	2.54 (0.24, 26.54)	0.48 (0.02, 10.63)	1.28 (0.21, 7.93)	0.86 (0.04, 17.46)	4.92 (0.24, 101.09)	(F2) imiquimod	0.08 (<0.005, 1.73)	0.06 (0.01, 0.28)
279.18 (5.58, 13970.12)	30 (0.95, 951.08)	5.61 (0.1, 310.02)	15.07 (0.66, 343.77)	10.09 (0.2, 520.18)	58.02 (1.12, 3007.15)	11.8 (0.58, 240.42)	(F4) ingenol	0.67 (0.03, 13.6)
414.45 (21.31, 8061.19)	44.53 (4.32, 459.3)	8.32 0.38, 184.46)	22.38 (3.66, 136.75)	14.98 (0.74, 302.98)	86.14 (4.23, 1754.46)	17.52 (3.51, 87.41)	1.48 (0.07, 29.96)	(J) placebo/sham

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy; INF=interferon

Table 20. Relative odds ratios for lack of histological clearance between individual interventions (all BCC lesions, two more subgraphs).

(A_plus_E1) surgery + PDT (MAL)	2.29 (0.32, 16.51)	1 (0.18, 5.68)	2.57 (0.36, 18.33)
0.44 (0.06, 3.16)	(A_plus_E1_plus_H) surgery + PDT (MAL) + curettage	0.44 (0.06, 3.16)	1.13 (0.13, 9.94)
1 (0.18, 5.68)	2.29 (0.32, 16.51)	(A_plus_E2) surgery + PDT (MAL)	2.57 (0.36, 18.33)
0.39 (0.05, 2.77)	0.89 (0.1, 7.86)	0.39 (0.05, 2.77)	(A_plus_E2_plus_H) surgery + PDT (MAL) + curettage

(C5) laser	0.02 (<0.005, 0.56)	0.17 (0.03, 0.9)
43.95 (1.77, 1090.16)	(F5) other medical	7.49 (0.29, 196.65)
5.87 (1.11, 31.13)	0.13 (0.01, 3.51)	(I) no treatment

Table 21. Relative odds ratios for lack of histological clearance between individual interventions (all BCC lesions, two more subgraphs).

(F2_plus_H) imiquimod + curettage	0.17 (0.01, 1.88)		
6.00 (0.53, 67.65)	Curettage (H)		
		MMS (B)	11.11 (2.66, 46.36)
		0.09 (0.02, 0.38)	(B_plus_F2) MMS + imiquimod

Table 22. Mean and forecasted lack of histological clearance fractions by intervention category (all BCC lesions).

Intervention type	Mean lack of histological clearance fraction (95% CI)	Forecasted lack of histological clearance fraction (95% CI)
First subgraph		
Surgical excision (A)	1.2 (0.1, 15.8)	1.2 (<0.5, 36.3)
Cryotherapy (C1)	10.1 (1.4, 46.4)	10.1 (0.4, 76.9)
Laser (C5+E1) + PDT (MAL)	37.5 (3.2, 91.5)	37.5 (1.1, 96.9)
PDT (MAL) (E1)	18.2 (5.1, 48.0)	18.2 (1.0, 82.5)
PDT (ALA) (E2)	25.0 (2.0, 84.4)	25.0 (0.7, 94.2)
5-FU (F1)	5.5 (0.4, 48.7)	5.5 (0.1, 73.9)
Imiquimod (F2)	22.2 (8.3, 47.3)	22.2 (1.5, 84.3)
Ingenol (F4)	77.1 (17.2, 98.2)	77.1 (6.5, 99.4)
Placebo (J)	83.3 (61.9, 93.9)	83.3 (21.1, 98.9)
Second subgraph		
Surgery + PDT (MAL) (A+E1)	36.4 (14.3, 66.1)	NA
Surgery + PDT (MAL) + curettage (A+E1+H)	20.0 (5.0, 54.1)	NA
Surgery + PDT (ALA) (A+E2)	36.4 (14.3, 66.1)	NA
Surgery + PDT (ALA) + curettage (A+E2+H)	18.2 (4.6, 50.7)	NA
Third subgraph		
Laser (C5)	43.5 (26.1, 62.8)	NA
Other medical (diclofenac and/or calcitriol) (F5)	97.1 (66.4 99.8)	NA
No treatment (J)	80.5 (58.8, 92.2)	NA
Fourth subgraph		
Imiquimod + curettage (F2+H)	10.0 (1.4, 46.7)	NA
Curettage (H)	40.0 (15.8, 70.3)	NA
Fifth subgraph		
MMS (B)	92.0 (75.8, 97.7)	NA
MMS + imiquimod (B+F2)	51.0 (37.0, 64.9)	NA

NA: forecasts are not available for the 4 smaller subgraphs, because they were analyzed with a fixed effects model. MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy.

Incomplete excision, all BCC lesions

Two RCTs reported incomplete excision outcomes in mixed BCC populations. In the first study, the average age was 68 (SD 12), and 39.7 percent were female. The average lesion size was 1.28 cm^2 (SD 1.36) in the group randomized to receive Mohs surgery (n=198) and 1.77 cm^2 (SD 1.28) in the surgical excision without intraoperative evaluation group (n=199). In this study, about half of the BCCs were classified as aggressive. After the first excision, 35 of 199 lesions (17.6%) were found to have been incompletely excised in the surgical excision without intraoperative margin assessment group; whereas none were found in the Mohs surgery group (0/198). Thirty-one of the lesions in the excision group were re-excised and of these four were found to have been incompletely excised (12.9%). In the aggressive lesions, the incomplete excision rate was 21 of 88 (23.9%) in the surgical excision group; none in the Mohs group (n=105).[77]

The second RCT reported incomplete excision and number of repeat procedures in people who had either surgical excision without intraoperative assessment of the margins or curettage and cryosurgery for BCCs on their face (90%) or trunk/neck (10%). The mean age was 67 (range 34 to 92), and 43 percent were women. In the curettage and cryosurgery group there were 51 lesions, all nodular, with an average diameter of 5.4 mm (SD 2.9). In the surgical excision arm, there were 49 lesions, 92 percent nodular and 8 percent superficial, with an average diameter of 5.3 mm (SD 2.6). There were no incomplete excisions in the curettage and cryosurgery group; and there were three in the surgical excision group (6%). There were no repeat procedures in the curettage and cryosurgery group and four in the surgical excision group.[18]

Lack of histological clearance, subgroup analyses by lesion type

We conducted subgroup analyses by the type of BCC lesion. We report analyses comparing groups of interventions, but not analyses comparing individual treatments. The latter are very sparse, and their results are very similar to the pertinent comparisons in Tables 19, 20, and 21.

Many subgroup analyses per lesion type are possible. In this section, we describe analyses in RCTs of lower-risk lesions (strata of predominantly [>80%] superficial BCCs, predominantly nodular BCCs, and superficial or nodular BCCs) overall, and broken down by lesion type, as well as higher-risk lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).

Fifteen RCTs (n=1972 lesions) included low-risk BCCs (nodular and superficial subtypes).[41, 45, 50, 51, 60, 62, 64-66, 88-90, 95, 97, 100] Their results are very similar to the findings in Tables 17 and 18 in the previous section.

With respect to RCT strata of predominantly superficial lesions, six RCTs (n=1300 lesions) compared PDT (E) versus drugs (F) versus no or sham treatment.[45, 51, 64, 65, 88, 90] These results are shown in Tables 23 and 24. Briefly, there was no statistically significant difference between the two active intervention categories, but both were statistically significantly better than no or sham treatment. The box provides details about the comparisons between these six RCTs.

Studies (total sample)	6 (1300)
Total sample by intervention	(E): 126; (F): 693; (I,J): 481
Total sample by intervention, (min, max)	126, 693
Data by comparison	(E--F): 1 (271); (F--I,J): 5 (1029)
Studies by comparison (min, max)	1, 5

Total sample by comparison (min, max)	271, 1029
Followup median (min, max)	3 (2, 36) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Table 23. Relative odds ratios for lack of histological clearance between intervention categories (predominantly superficial BCC lesions)

PDT (E)	0.19 (<0.005, 9.84)	0.01 (<0.005, 0.36)
5.17 (0.1, 263.01)	Drugs (F)	0.03 (<0.005, 0.36)
150.98 (2.78, 8187.95)	29.21 (2.81, 303.6)	No/sham treatment (I,J)

PDT=Photodynamic Therapy

Table 24. Mean fraction of lesions without histological clearance by intervention category (predominantly superficial BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
PDT (E)	7.9 (0.2, 75.9)	7.9 (0.1, 93.1)
Drugs (F)	30.8 (8.4, 68.3)	30.8 (0.9, 95.6)
No/sham treatment (I,J)	92.9 (69.8, 98.7)	92.9 (20.2, 99.9)

PDT=Photodynamic Therapy

With respect to the five RCT strata of predominantly nodular lesions (n=374),[41, 51, 62, 66, 89] the corresponding results are listed in Tables 25 and 26. These results are qualitatively similar to the corresponding results from the analyses in Tables 17 and 18. Details on the comparisons are in the box.

Studies (total sample)	5 (374)
Total sample by intervention	(F): 84; (I,J): 115; (A,B): 35; (E): 124; (C): 16
Total sample by intervention, (min, max)	16, 124
Data by comparison	(F--I,J): 2 (124); (I,J--E): 1 (150); (A,B--E): 1 (68); (E--C): 1 (32)
Studies by comparison (min, max)	1, 2
Total sample by comparison (min, max)	32, 150
Followup median (min, max)	3 (2, 12) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Table 25. Relative odds ratios for lack of histological clearance between intervention categories (nodular BCC lesions)

Surgery/MMS (A,B)	0.02 (<0.005, 1.48)	0.04 (<0.005, 1.79)	0.01 (<0.005, 0.44)	<0.005 (<0.005, 0.14)
42.6 (0.67, 2692.89)	Heat/cold (C)	1.9 (0.14, 26.18)	0.39 (0.02, 6.78)	0.14 (0.01, 1.99)
22.45 (0.56, 903.83)	0.53 (0.04, 7.27)	PDT (E)	0.21 (0.02, 1.76)	0.08 (0.01, 0.48)
108.35 (2.29, 5127.73)	2.54 (0.15, 43.87)	4.83 (0.57, 40.95)	Drugs (F)	0.36 (0.04, 3.13)

298.54 (7.35, 12122.67)	7.01 (0.5, 97.88)	13.3 (2.1, 84.38)	2.76 (0.32, 23.73)	No/sham treatment (I,J)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 26. Mean and forecasted lack of histological clearance fractions by intervention category (nodular BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
Surgery/MMS (A,B)	1.4 (<0.5, 31.0)	1.4 (<0.5, 44.0)
Heat/cold (C)	37.5 (5.8, 85.5)	37.5 (2.7, 92.8)
PDT (E)	24.0 (8.0, 53.6)	24.0 (2.7, 78.1)
Drugs (F)	60.4 (21.8, 89.3)	60.4 (9.6, 95.6)
No/sham treatment (I,J)	80.8 (52.9, 94.0)	80.8 (26.9, 98.0)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy; INF=interferon

Incomplete excision (a related outcome) in high-risk BCCs

We identified one RCT that measured the distinct, yet related, outcome of incomplete excision in 172 lesions, about half of which were on the face, the rest were elsewhere on the body. This study compared surgical excision (A) with MMS (B) in histologically aggressive facial lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation). The average age was 65 years (standard deviation 13), and 43.3 percent were female. The average lesion diameter was 9.1 mm (standard deviation 4.1). In the 88 lesions that had surgical excision without intraoperative margin assessment, two had an incomplete excision. This outcome was not applicable to the other arm of the study (ALA-PDT).[19]

Lack of histological clearance, other subgroup analyses (lesion location, lesion size, sex, age)

Table 27 below shows results on subgroup analyses for two RCTs that reported treatment effects in subgroups of interest. The first RCT enrolled patients with predominantly superficial BCCs and found significant differences in treatment effects across a number of subgroups that include age, gender, lesion location, and lesion size.[45, 83, 84] The second RCT reported subgroup results for lack of histological clearance in predominantly nodular BCC. There was no significant difference between or within subgroups based on lesion location or size.[62]

Table 27. Subgroup results for lack of histological clearance in superficial BCCs

Study	Comparison	Timepoint	Subgroup	n/N arm 1 vs. n/N arm 2	OR (95% CI); P-Value Within	P- Value Between
Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	age: <= 60 years old	25/81 vs. 8/77	3.85 (1.61, 9.20); p=0.002	p=0.032
			age: > 60 years old	27/115 vs. 23/112	1.19 (0.63, 2.23); p=0.633	
Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	females	29/103 vs. 9/92	3.61 (1.61, 8.13); p=0.002	p=0.029
			males	23/93 vs. 22/97	1.12 (0.57, 2.19); p=0.865	

Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	lesion location: head/neck	9/24 vs. 4/20	2.40 (0.61, 9.47); p=0.047	p=0.321
			lesion location: trunk	36/115 vs. 12/116	3.95 (1.93, 8.08); p<0.001	
			lesion location: lower extremities	2/26 vs. 6/28	0.31 (0.06, 1.68); p=0.253	
			lesion location: upper extremities	5/31 vs. 3/25	1.41 (0.30, 6.58); p=0.720	
Arits 2013 23683751	PDT (MAL) (E1) vs. Imiquimod (F2)	12 months	lesion area: <= 60 mm2	23/106 vs. 18/90	1.11 (0.55, 2.22); p=0.861	p=0.043
			lesion area: > 60 mm2	27/86 vs. 12/96	3.20 (1.50, 6.83); p=0.002	
Foley 2009 20064185	PDT (MAL) (E1) vs. sham PDT (J)	3 months	lesion location: extremities	5/15 vs. 12/17	0.21 (0.05, 0.93); p=0.074	p=0.437
			lesion location: face/scalp	3/19 vs. 18/23	0.05 (0.01, 0.25); p<0.001	
			lesion location: neck	4/9 vs. 1/1	0.27 (0.01, 8.46); p=1.000	
			lesion location: trunk	8/32 vs. 24/34	0.14 (0.05, 0.41); p<0.001	
Foley 2009 20064185	PDT (MAL) (E1) vs. sham PDT (J)	3 months	lesion diameter: <10 mm	15/64 vs. 43/61	0.13 (0.06, 0.28); p<0.001	p=0.939
			lesion diameter: 10-20 mm	5/11 vs. 12/14	0.14 (0.02, 0.94); p=0.081	

NA = not significant; PDT = photodynamic therapy

Lack of histological clearance, results from non-randomized studies (BCC lesions)

We identified six NRCSs reporting lack of histological clearance in BCC or mixed BCC and SCC lesions.[139, 146-150] These are summarized narratively below.

The first NRCS included 12 patients with one superficial BCC each. After an initial excision surgery, six patients received imiquimod and six received placebo. The study was deemed to be at a high risk of confounding bias, because the arms were not balanced (there were only six patients per arm); both the dermatologist and pathologist were blinded, and the study followed all participants to the end. The mean lesion area was 52 mm^2, and the lesions were located on the trunk or neck (67%) or forearm (33%). The mean age was 61 (range 52 to 78), and 33 percent were female. All lesions in the vehicle group had residual tumor at excision, as did four of the six treated with imiquimod.[150]

The second NRCS reported lack of clinical and histological clearance in 74 patients with one nodular BCC each, receiving different doses of vismodegib. The risk of bias of this study was judged to be moderate because of lack of blinding and inadequate baselines reporting that lead to ambiguity about how well balanced the arms were. The lesion diameter ranged from 1 to 3 cm, and all were located in the scalp, head, neck, trunk, or limbs. The mean age was 63.6 (SD 12; range 40 to 89), and 22 percent were female; 99 percent were white. Twenty-four lesions were treated with vismodegib for 12 weeks then were excised; twenty-five were treated with vismodegib for 12 weeks then had a 24-week observation period before excision; and 25 were treated with vismodegib for 16 weeks then were excised. The 12-week groups had a much higher and statistically significant rate of lack of clinical clearance than the 16-week group (OR 10.42; 95% CI 1.22 to 89.13).

However, the lack of histological clearance was much closer between the two doses, and not significant (OR 1.57; 95% CI 0.49 to 5.01).[149]

The third NRCS reported on lack of histological clearance in 56 people with 56 nodular BCCs, who received ALA-PDT with or without surface preparation with a CO2 laser. This study was judged to have moderate to low risk of bias, primarily because of lack of blinding. The mean age was 62, and 43 percent were females. Most of the lesions (87.5%) were on the head (not H-zone or adjacent to the eyes or ears) or neck. The group with the surface preparation had a lower rate of lack of histological clearance than the group without surface preparation (OR 0.23; 95% CI 0.07 to 0.75).[146]

The fourth NRCS reported on a matched population of 40 patients treated with different doses of brachytherapy (36.6 versus 42 Gy). This study was deemed to be at a moderate risk of confounding bias, primarily for lack of blinding and unclear reporting of baselines. The mean age was 75, 45 percent were female, and all had a Fitzpatrick skin score of I (47.5%) or II (52.5%). Forty-five percent of the BCCs were superficial, while 55 percent were nodular; 75 percent were on the head and neck and 25 percent on the trunk or extremities. The lower dose (36.6 Gy) had a higher rate of lack of histological clearance at up to a year than the higher dose (42 Gy), but this difference was not significant (OR 2.11; 95% CI 0.18 to 25.35).[139]

The fifth NRCS reports on 20 BCC lesions (43% superficial/multicentric, 47.5% nodular, 9.5% infiltrative/micronodular/morpheaform/sclerosing; 90.5% on the trunk/neck and 9.5% on the extremities) treated with pulse dye laser and 20 matched lesions that received no treatment. This study was deemed to be at a moderate risk of confounding bias, primarily for lack of blinding and unclear reporting of baselines. At surgical excision, approximately 2 weeks after the last treatment, 7 of the 20 lesions treated with pulse dye laser showed lack of histological clearance, compared to 18 of the lesions not treated (OR 0.06; 95% CI 0.01 to 0.34).[148]

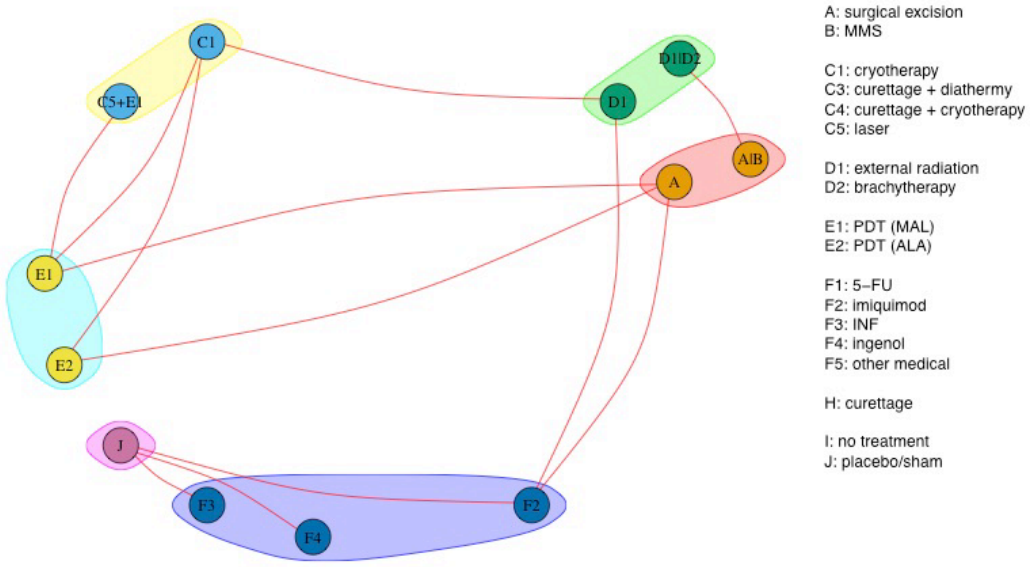
Finally, the sixth NRCS included both BCCs (71%) and SCCs (29%), and compared two doses of external radiation therapy. In the lower-dose (37 Gy) group 14 of 236 lesions (5.9%) were not histologically clear compared to none of 149 (0%) in the higher-dose (45 Gy) group. There was no adjusted analysis available for this outcome.[147]

Lack of clinical clearance (all BCC lesions)

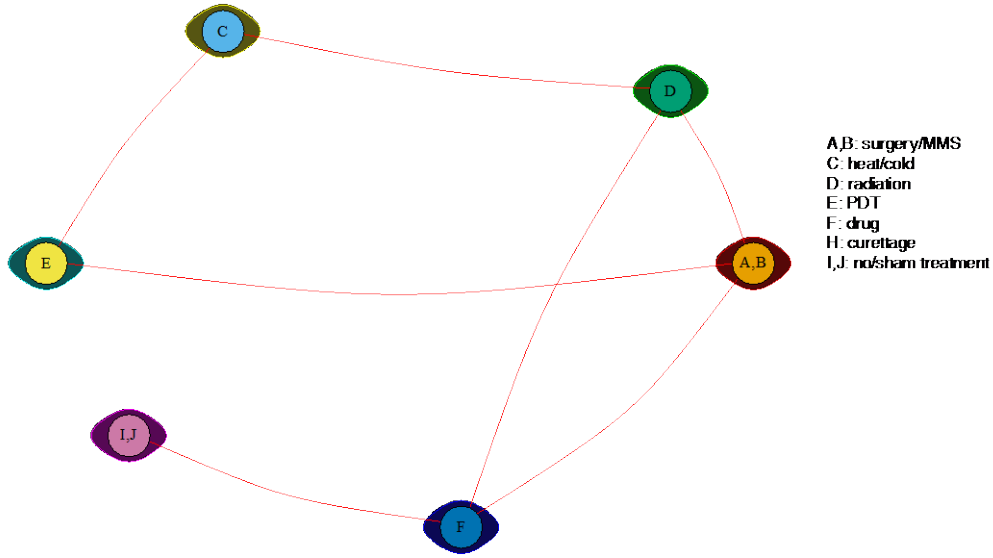
The evidence graph for lack of clinical clearance with respect to individual treatments is sparse (Figure 6 [C] – reproduced in Figure 9 [A] for ease of reference), and comprises 3 connected subgraphs. Detailed results at the RCT-level are in the appendix.

Figure 9: Evidence graph of RCTs evaluating lack of clinical clearance in BCCs across (A) individual interventions and types of interventions (B).

(A)



(B)



Note that the evidence graph for the individual treatments comprises 2 connected subgraphs defined by D1|D2, A|B; and the set of all remaining nodes.

Comparisons across intervention categories

In total, 14 RCTs (1734 lesions) were included in this analysis.[43, 46-49, 54, 55, 63, 66, 81, 88, 90, 94, 100] Twelve RCTs were deemed to be at low or moderate risk of bias. Cumulative sample sizes per comparison ranged from 27 to 380; for more details see the box below.

Studies (total sample)	14 (1734)
Total sample by intervention	(D): 201; (F): 379; (A,B): 460; (C): 189; (I,J): 129; (E): 376
Total sample by intervention, (min, max)	129, 460
Data by comparison	(D--F): 1 (27); (D--A,B): 1 (347); (D--C): 1 (31); (F--A,B): 1 (212); (F--I,J): 3 (379); (A,B--E): 3 (380); (C--E): 4 (358)
Studies by comparison (min, max)	1, 4
Total sample by comparison (min, max)	27, 380
Followup median (min, max)	6 (3, 41) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Table 28 shows the relative odds ratios for lack of clinical clearance across intervention categories. Overall, no or sham treatment (I,J) was statistically significantly worse than all active treatments. Surgical treatments (A,B) were statistically significantly better than PDT (E) and drugs (F) All other comparisons were statistically not significant; however, the confidence intervals were wide and could not exclude even large differences between the comparators.

In the Table, shaded cells correspond comparisons that have been inferred from the analysis model, but that have not been examined in the included RCTs. For example, comparisons of surgical treatments (A,B) versus drugs (F) are indirect. Indirect comparisons are more uncertain that those for which head-to-head data exist. The added uncertainty about indirect comparisons is partly reflected in the width of the respective 95% confidence intervals, which is (often much) broader for comparisons without versus with direct data. For all comparisons that are empirically observed (all non-shaded cells in the Table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 28 (see Appendix I).

Table 28. Relative odds ratios for lack of clinical clearance between intervention categories (all BCC lesions)

Surgery/MMS (A,B)	0.28 (0.05, 1.54)	0.63 (0.07, 5.37)	0.18 (0.04, 0.74)	0.15 (0.03, 0.9)	0.01 (<0.005, 0.04)
3.61 (0.65, 20.03)	Heat/cold (C)	2.27 (0.27, 19.38)	0.65 (0.19, 2.24)	0.55 (0.09, 3.34)	0.02 (<0.005, 0.16)
1.59 (0.19, 13.65)	0.44 (0.05, 3.77)	Radiation (D)	0.29 (0.04, 2.28)	0.24 (0.03, 2.18)	0.01 (<0.005, 0.10)
5.55 (1.35, 22.71)	1.54 (0.45, 5.28)	3.48 (0.44, 27.62)	PDT (E)	0.84 (0.16, 4.4)	0.03 (<0.005, 0.22)
6.58 (1.11, 38.87)	1.82 (0.3, 11.1)	4.13 (0.46, 37.14)	1.19 (0.23, 6.2)	Drugs (F)	0.04 (0.01, 0.15)
178.93 (22.57, 1418.56)	49.53 (6.25, 392.28)	112.26 (9.83, 1282.56)	32.26 (4.63, 224.58)	27.19 (6.7, 110.38)	No/sham treatment (I,J)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 29 offers complementary information from the same analysis. For each intervention catgory, it shows the mean fraction of lesions without clinical clearance across the included RCTs. It also forecasts expected fractions with each intervention category in groups of patients similar to the patients included in the analyzed RCTs. The average percentage of lesions with no clinical clearance was 2.9 percent in surgical treatment arms, between 4.5 and 16.5 percent in other active intervention categories, and 84.2 percent for no or sham treatment.

Table 29. Mean and forecasted lack of clinical clearance fractions by intervention category (all BCC lesions).

Intervention type	Mean lack of clinical clearance fraction percent (95% CI)	Forecasted lack of clinical clearance fraction percent (95% CI)
Surgery/MMS (A,B)	2.9 (0.7, 10.7)	2.9 (0.1, 40.2)
Heat/cold (C)	9.7 (2.9, 27.9)	9.7 (0.5, 69.8)
Radiation (D)	4.5 (0.7, 23.6)	4.5 (0.2, 57.8)
PDT (E)	14.2 (5.4, 32.6)	14.2 (0.8, 76.6)
Drugs (F)	16.4 (5.0, 42.3)	16.4 (0.9, 81.1)
No/sham treatment (I,J)	84.2 (50.6, 96.5)	84.2 (17.3, 99.3)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Comparisons across individual interventions

The results of the analyses of intervention categories are congruent with the corresponding results of analyses of individual interventions. As evident from Figure 9, there are 2 connected subgraphs for this outcome. Separate analyses are conducted for each connected subgraph. In total, 14 RCTs (1734 lesions) were included in these analyses, as summarized in the box:

	First subgraph[43, 47-49, 54, 55, 63, 66, 81, 88, 90, 94, 100]	Second subgraph[46]
Studies (total sample)	13 (1387)	1 (347)
Total sample by intervention	(D1): 28; (F2): 213; (C1): 152; (F3): 118; (J): 129; (E2): 65; (A): 286; (E1): 311; (F4): 48; (C5+E1): 37	(A|B): 174; (D1|D2): 173
Total sample by intervention, (min, max)	28, 311	173, 174
Data by comparison	(D1--F2): 1 (27); (D1--C1): 1 (31); (F2--J): 1 (166); (F2--A): 1 (212); (C1--E2): 1 (83); (C1--E1): 1 (201); (F3--J): 1 (159); (J--F4): 1 (54); (E2--A): 1 (40); (A--E1): 2 (340); (E1--C5+E1): 2 (74)	(A|B--D1|D2): 1 (347)
Studies by comparison (min, max)	1, 2	1, 1
Total sample by comparison (min, max)	27, 340	347, 347
Followup median (min, max)	6 (3, 12) months	41 (41, 41) months

A: surgical excision, B: Mohs Micrographic Surgery; C1: cryotherapy; C3: diathermy and curettage; C4: cryotherapy and curettage; C5: laser; D1: external radiation; E1: MAL photodynamic therapy; E2: ALA photodynamic therapy; F1: 5-FU; F2: Imiquimod; F3: Interferon; F4: Ingenol; H: curettage; J placebo.

Table 30 has results on the relative effects for the largest subgraph. Table 31 has the corresponding results for the comparison of surgical excision or MMS (A|B) with external radiation therapy or brachytherapy (D1|D2). In Table 30 comparisons across individual observations are sparse; the majority of the pairwise comparisons are inferred from indirect data. The confidence intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the comparators. The comparison in Table 31 was not statistically significant; the confidence interval was wide and could not exclude large differences between the comparators.

Table 32 shows, for each intervention, the mean fractions for lack of clinical clearance across all RCTs. Estimates for interventions in all three subgraphs are listed in the Table. One should not statistically compare these fractions across the subgraphs, because they come from disjoint analyses. In general, the mean fractions of lack of clinical clearance for individual interventions are in congruence with the corresponding fractions estimated for intervention categories.

Table 30. Relative odds ratios for lack of clinical clearance between individual interventions (all BCC lesions, largest subgraph).

Surgery (A)	0.15 (0.04, 0.6)	1.1 (0.19, 6.39)	0.54 (0.04, 7.57)	0.17 (0.05, 0.59)	0.38 (0.11, 1.27)	0.43 (0.08, 2.2)	0.13 (0.02, 0.90)	0.02 (<0.005, 0.22)	0.01 (<0.005, 0.04)
6.83 (1.66, 28.13)	Cryotherapy (C1)	7.52 (1.4, 40.38)	3.69 (0.3, 45.29)	1.13 (0.35, 3.62)	2.58 (0.68, 9.83)	2.93 (0.52, 16.6)	0.92 (0.13, 6.45)	0.13 (0.01, 1.53)	0.05 (0.01, 0.31)
0.91 (0.16, 5.27)	0.13 (0.02, 0.71)	Laser + PDT (MAL) (C5+E1)	0.49 (0.03, 8.12)	0.15 (0.04, 0.54)	0.34 (0.05, 2.21)	0.39 (0.05, 2.89)	0.12 (0.01, 1.09)	0.02 (<0.005, 0.25)	0.01 (<0.005, 0.05)
1.85 (0.13, 25.95)	0.27 (0.02, 3.33)	2.04 (0.12, 33.78)	External radiation (D1)	0.31 (0.02, 3.95)	0.7 (0.05, 10.12)	0.79 (0.06, 10.69)	0.25 (0.02, 3.99)	0.03 (<0.005, 0.86)	0.01 (<0.005, 0.2)
6.04 (1.68, 21.7)	0.88 (0.28, 2.83)	6.66 (1.86, 23.84)	3.26 (0.25, 42.1)	PDT (MAL) (E1)	2.28 (0.55, 9.49)	2.59 (0.5, 13.45)	0.81 (0.12, 5.27)	0.11 (0.01, 1.27)	0.04 (0.01, 0.25)
2.65 (0.79, 8.94)	0.39 (0.1, 1.48)	2.92 (0.45, 18.8)	1.43 (0.1, 20.73)	0.44 (0.11, 1.83)	PDT (ALA) (E2)	1.14 (0.19, 6.88)	0.36 (0.05, 2.69)	0.05 (<0.005, 0.64)	0.02 (<0.005, 0.13)
2.33 (0.45, 11.99)	0.34 (0.06, 1.94)	2.57 (0.35, 19.1)	1.26 (0.09, 16.97)	0.39 (0.07, 2)	0.88 (0.15, 5.33)	Imiquimod (F2)	0.31 (0.09, 1.13)	0.04 (<0.005, 0.43)	0.02 (0.01, 0.05)
7.46 (1.12, 49.86)	1.09 (0.16, 7.7)	8.21 (0.92, 73.51)	4.03 (0.25, 64.75)	1.23 (0.19, 8.03)	2.81 (0.37, 21.32)	3.2 (0.88, 11.56)	INF (F3)	0.14 (0.01, 1.46)	0.06 (0.02, 0.13)
53.69 (4.47, 645.4)	7.86 (0.65, 94.85)	59.12 (4.07, 858.87)	28.99 (1.17, 719.78)	8.88 (0.79, 100.47)	20.26 (1.56, 262.75)	23.01 (2.33, 227.63)	7.2 (0.68, 75.65)	Ingenol (F4)	0.4 (0.04, 3.64)
135.5 (23.38, 785.42)	19.84 (3.21, 122.78)	149.23 (18.68, 1191.87)	73.18 (5.01, 1068.28)	22.42 (3.95, 127.34)	51.13 (7.68, 340.6)	58.08 (21.77, 154.91)	18.17 (7.52, 43.89)	2.52 (0.27, 23.19)	Placebo (J)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy; INF=Interferon

Table 31. Relative odds ratios for lack of clinical clearance between individual interventions (all BCC lesions, remaining subgraphs).

Surgery or MMS (A|B)	0.16 (0.01, 3.27)
6.16 (0.31, 123.87)	External radiation or brachytherapy (D1|D2)

Table 32. Mean and forecasted lack of clinical clearance fractions by individual intervention (all BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
First subgraph		
Surgical excision (A)	3.3 (0.9, 11.3)	3.3 (0.2, 41.4)
Cryotherapy (C1)	19.0 (6.3, 44.9)	19.0 (1.2, 82.4)
Laser + PDT (MAL) (C5+E1)	3.0 (0.6, 13.1)	3.0 (0.1, 42.1)
External radiation (D1)	6.0 (0.6, 41.9)	6.0 (0.2, 71.0)
PDT (MAL) (E1)	17.2 (6.5, 38.5)	17.2 (1.1, 79.7)
PDT (ALA) (E2)	8.4 (2.2, 27.2)	8.4 (0.4, 66.2)
Imiquimod (F2)	7.4 (2.0, 23.9)	7.4 (0.4, 62.8)
IFN(F3)	20.4 (4.9, 56.0)	20.4 (1.1, 85.8)
Ingenol (F4)	64.9 (17.1, 94.3)	64.9 (5.3, 98.4)
No/sham treatment (J)	82.3 (52.3, 95.2)	82.3 (17.6, 99.0)
Second subgraph		
Surgical excision or MMS (A|B)	0.3 (0.0, 4.4)	NA
External radiation or brachytherapy (D1|D2)	1.7 (0.6, 5.2)	NA

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Lack of clinical clearance, subgroup analyses by lesion type

We conducted subgroup analyses by the type of BCC lesion. We report analyses comparing groups of interventions, but not analyses comparing individual treatments. The latter are very sparse, and their results are similar to the pertinent comparisons in Tables 30 and 31.

Many subgroup analyses per lesion type are possible; we describe here analyses in RCTs of lower-risk lesions (strata of predominantly [>80%] superficial BCCs, predominantly nodular BCCs, and superficial or nodular BCCs) overall, and broken down by lesion type, along with analyses of higher-risk lesions (morpheaform, micronodular, trabecular, infiltrative, or squamous differentiation).

All 14 RCTs reporting results on lack of clinical clearance enrolled patients with low-risk BCCs (nodular and superficial subtypes; n=1922).[43, 46-49, 54, 55, 63, 66, 81, 88, 90, 94, 100] Thus, for the lower-risk BCCs subgroup the results are practically the same as in the previous section (Tables 28 and 29).

Tables 33 and 34 show results of five RCTs of patients with predominantly superficial BCC lesions (n=868).[47, 48, 88, 90, 94] Most comparisons in Table 33 are indirect, and the confidence intervals for these differences are too broad to allow drawing conclusions. The box summarizes characteristics of these comparisons:

Studies (total sample)	5 (868)
Total sample by intervention	(F): 246; (I,J): 88; (A,B): 215; (E): 221; (C): 98
Total sample by intervention, (min, max)	88, 246
Data by comparison	(F--I,J): 2 (220); (F--A,B): 1 (212); (A,B--E): 1 (235); (E--C): 1 (201)
Studies by comparison (min, max)	1, 2
Total sample by comparison (min, max)	201, 235
Followup median (min, max)	3 (3, 36) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Table 33. Relative odds ratios for lack of clinical clearance between intervention categories (superficial BCC lesions)

Surgery/MMS (A,B)	0.13 (<0.005, 10.81)	0.12 (<0.005, 5.06)	0.02 (<0.005, 0.79)	<0.005 (<0.005, 0.02)
7.71 (0.09, 642.49)	Heat/cold (C)	0.94 (0.01, 59.67)	0.19 (<0.005, 9.58)	<0.005 (<0.005, 0.28)
8.16 (0.2, 337.33)	1.06 (0.02, 66.93)	PDT (E)	0.2 (0.01, 4.49)	<0.005 (<0.005, 0.14)
40.1 (1.27, 1269.18)	5.2 (0.1, 259.27)	4.91 (0.22, 108.22)	Drugs (F)	0.02 (<0.005, 0.53)
2071.45 (41.73, 102817.08)	268.7 (3.6, 20036.53)	253.71 (7.01, 9177.18)	51.65 (1.88, 1415.99)	No/sham treatment (I,J)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 34. Mean and forecasted lack of clinical clearance fractions by intervention category (superficial BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
Surgery/MMS (A,B)	0.7 (<0.5, 10.7)	0.7 (<0.5, 34.6)
Heat/cold (C)	5.1 (0.2, 61.3)	5.1 (<0.5, 85.5)
PDT (E)	5.4 (0.5, 38.5)	5.4 (0.1, 76.5)
Drugs (F)	21.9 (3.8, 66.4)	21.9 (0.6, 92.6)
No/sham treatment (I,J)	93.5 (50.0, 99.5)	93.5 (17.6, 99.9)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

The results for six RCTs of predominantly nodular lesions (n=434) are listed in Tables 35 and 36.[48, 49, 54, 63, 66, 81] These results very uncertain, and are based on at most two studies per comparison. The confidence intervals for differences between the intervention categories are generally very broad. The box provides details on the comparisons of these RCTs.

Studies (total sample)	6 (434)
Total sample by intervention	(D): 12; (F): 113; (A,B): 161; (E): 111; (C): 37
Total sample by intervention, (min, max)	12, 161
Data by comparison	(D--F): 1 (27); (F--A,B): 1 (188); (A,B--E): 2 (145); (E--C): 2 (74)
Studies by comparison (min, max)	1, 2
Total sample by comparison (min, max)	27, 188
Followup median (min, max)	8 (3, 36) months

Table 35. Relative odds ratios between intervention categories for lack of clinical clearance (nodular BCC lesions)

Surgery/MMS (A,B)	2.06 (0.38, 11.25)	1.79 (0.03, 97.08)	0.28 (0.09, 0.87)	1.98 (0.15, 26.6)
0.49 (0.09, 2.65)	Heat/cold (C)	0.87 (0.01, 53.43)	0.13 (0.04, 0.49)	0.96 (0.06, 16.76)
0.56 (0.01, 30.25)	1.15 (0.02, 70.67)	Radiotherapy (D)	0.15 (<0.005, 8.16)	1.11 (0.03, 44.12)
3.63 (1.16, 11.4)	7.48 (2.06, 27.14)	6.5 (0.12, 344.91)	PDT (E)	7.19 (0.52, 99.37)
0.5 (0.04, 6.77)	1.04 (0.06, 18.11)	0.9 (0.02, 36.04)	0.14 (0.01, 1.92)	Drugs (F)

RCTs of predominantly nodular lesions

Table 36. Mean fractions of lesions with no clinical clearance by intervention category (nodular BCC lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
Surgery/MMS (A,B)	7.6 (1.5, 31.6)	7.6 (0.2, 74.7)
Heat/cold (C)	3.9 (0.6, 20.6)	3.9 (0.1, 60.6)
Radiotherapy (D)	4.4 (0.1, 66.7)	4.4 (0.0, 86.1)
PDT (E)	23.0 (6.0, 58.5)	23.0 (0.9, 90.8)
Drugs (F)	4.0 (0.4, 32.7)	4.0 (0.1, 69.1)

RCTs of predominantly nodular lesions

Lack of clinical clearance, other subgroup analyses (lesion location, lesion size)

Table 37 below shows results on subgroup analyses for three RCTs that reported treatment effects in subgroups of interest, two in patients with predominantly superficial BCCs[47, 94] and one in patients with predominantly nodular BCCs.[21, 81] Neither lesion location nor size were associated with differences in the treatment effect beyond what is expected by chance. Only one outcome was statistically significant at a 0.05 level: surgical excision (A) performed better than PDT with MAL (E1) for lesions on the trunk and neck at 3 months; however by 12 months, this finding was no longer significant.[94]

Table 37. Subgroup results for lack of clinical clearance in BCC lesions.

Study	Comparison	Timepoint	Subgroup	n/N arm 1 vs. n/N arm 2	OR (95% CI); P-Value Within	P- Value Between
Szeimies 2008 18624842	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion location: face/scalp	0/4 vs. 0/15	N/A	NA
			lesion location: trunk/neck	1/83 vs. 7/76	0.12 (0.01, 1.00) ; p=0.028	
			lesion location: extremities	0/31 vs. 3/37	0.16 (0.01, 3.15); p=0.245	
Szeimies 2008 18624837	Surgical excision (A) vs. PDT (MAL) (E1)	12 months	lesion location: face/scalp	0/4 vs. 4/15	0.28 (0.01, 6.42); p=0.530	NA
			lesion location: trunk/neck	0/82 vs. 3/69	0.12 (0.01, 2.27); p=0.093	
			lesion location: extremities	0/31 vs. 4/34	0.11 (0.01, 2.08); p=0.115	
Rhodes 2004 14732655	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion location: extremities	0/5 vs. 0/5	NA	NA
			lesion location: face/scalp	1/32 vs. 1/21	0.65 (0.04, 10.91); p=1.000	
			lesion location: trunk/neck	0/15 vs. 4/27	0.17 (0.01, 3.35); p=0.279	
Szeimies 2008 18624840	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion diameter: 7-14 mm	1/70 vs. 7/85	0.16 (0.02, 1.35); p=0.073	NA
			lesion diameter: 15-20 mm	0/43 vs. 3/43	0.13 (0.01, 2.66); p=0.241	

Rhodes 2004 14732655	Surgical excision (A) vs. PDT (MAL) (E1)	3 months	lesion diameter: 6-14mm	1/43 vs 4/40	0.21 (0.02, 2.00); p=0.191	p=0.994
			lesion diameter: 15-19mm	0/6 vs. 1/11	0.54 (0.02, 15.30); p=1.000	
			lesion diameter: 20-30mm	0/3 vs. 0/2	NA	
Basset-Seguin 2008 18693159	Cryotherapy (C1) vs. PDT (MAL) (E1)	3 months	lesion diameter: 5-10mm	3/41 vs. 1/44	3.39 (0.34, 34.02); p=0.349	NA
			lesion diameter: 11-19 mm	2/41 vs. 1/43	2.15 (0.19, 24.70); p=0.611	
			lesion diameter: >= 20 mm	0/16 vs. 1/16	0.31 (0.01, 8.28); p=1.000	

NA = not significant; PDT = photodynamic therapy

Lack of clinical clearance, results from non-randomized studies (BCC lesions)

None of the eligible NRCSs reported data on lack of clinical clearance.

Various outcomes in patients with high-risk lesions treated with hedgehog inhibitors, BBC lesions

Hedgehog inhibitors, including vismodegib and sonidegib (F5, other drugs), are a group of systemic medications that are primarily used for advanced or metastatic BCC. Comparisons of outcomes in these high-risk populations with studies that include lower-risk BCCs are not clinically meaningful and so we report these separately.

One RCT (n=230) compared 2 doses (200 vs. 800 mg per os daily) of sonidegib for locally advanced BCC not amenable to surgery (n=194) or radiation or metastatic BCC for which other options had been exhausted (n=36). Median age was 67 and 65, respectively, and over 90 percent were white. In the locally advanced group, 2 of 66 (3%) participants in the 200 mg arm achieved a complete response compared with none of 128 (0%) in the 800 mg arm. The number of participants experiencing any adverse event was high in both arms (75/79 [95%] in the 200 mg arm, 150/150 [100%] in the 800 mg arm.[71]

Patient-reported cosmetic outcomes, all BCC lesions

For this outcome we describe only results between intervention categories, because data are sparse for the comparison of individual observations. In total, seven RCTs (752 lesions) were included in this analysis.[46, 47, 63, 66, 81, 94, 95] Five RCTs were deemed to be at low or moderate risk of bias. The evidence graph in Figure 10 shows the observed comparisons based on RCTs that report patient assessments of "at least good" cosmetic outcome. The evidence graph is sparsely connected. Patients assessed cosmetic outcomes using different scales in each RCT, though often on scales of that included poor, fair, good, and excellent or similar. We provide analyses for an "at least good" cosmetic outcome. Details about the comparisons between these RCTs are in the box:

Studies (total sample)	7 (752)
Total sample by intervention	(D): 125; (F): 15; (A,B): 309; (C): 113; (E): 190
Total sample by intervention, (min, max)	15, 309
Data by comparison	(D--F): 1 (27); (D--A,B): 1 (244); (A,B--C): 1 (96); (A,B--E): 2 (254); (C--E): 2 (131)
Studies by comparison (min, max)	1, 2
Total sample by comparison (min, max)	27, 254
Followup median (min, max)	4 (3, 48) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Figure 10. Evidence graph of RCTs comparing patient-assessed cosmetic outcomes (all BCC lesions)

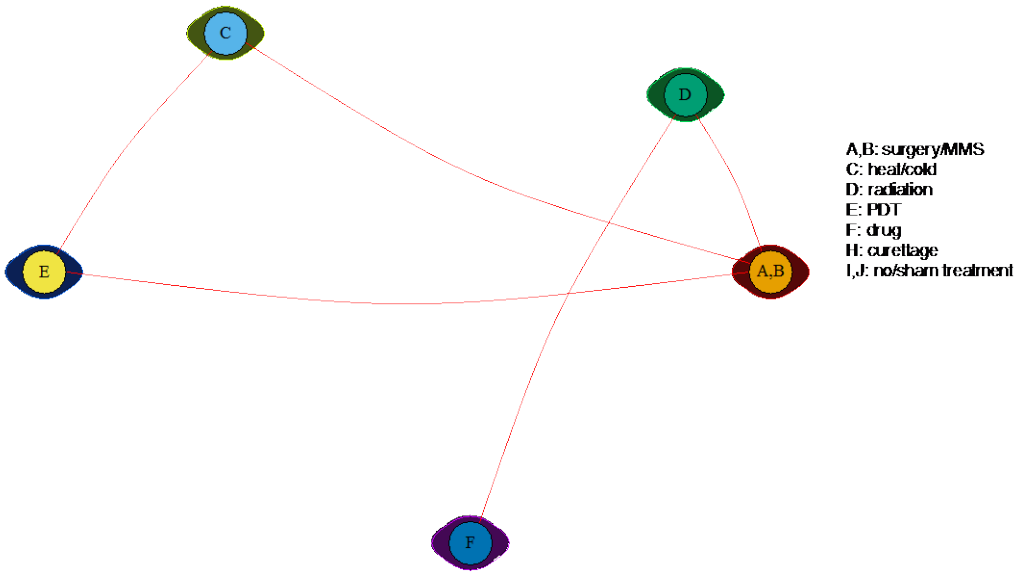


Table 38 shows the results of the comparisons between intervention categories based on a network meta-analysis. Most comparisons are indirect (denoted by shaded cells) and have wide confidence intervals. For comparisons with head-to-head data (denoted by unshaded cells) the

numbers in the table are very similar whether information from indirect comparisons is included or excluded. Five of 10 comparisons are statistically significant.

Table 38. Relative odds ratios between intervention categories for at least good cosmetic outcome as assessed by patients (all BCC lesions)

Surgery/MMS (A,B)	5.2 (1.37, 19.79)	2.1 (1.18, 3.72)	0.17 (0.06, 0.46)	0.49 (0.02, 14.01)
0.19 (0.05, 0.73)	Heat/cold (C)	0.4 (0.1, 1.67)	0.03 (0.01, 0.13)	0.09 (<0.005, 3.01)
0.48 (0.27, 0.85)	2.48 (0.6, 10.25)	Radiation (D)	0.08 (0.02, 0.25)	0.23 (0.01, 6.69)
6 (2.16, 16.69)	31.19 (7.54, 128.97)	12.58 (3.95, 40.03)	PDT (E)	2.95 (0.09, 93.05)
2.03 (0.07, 58.01)	10.58 (0.33, 336.76)	4.27 (0.15, 121.7)	0.34 (0.01, 10.7)	Drugs (F)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 39 shows the average percentage of patients with at least good cosmetic outcomes in the RCTs, based on the same network meta-analysis as the Table above. Drugs (F) and PDT (E) are associated with highest percentages, followed surgical treatments (A,B), radiation (D), interventions that use heat or cold to destroy the lesion (C).

Table 39. Mean and forecasted fractions of lesions with at least good cosmetic outcome as assessed by patients (all BCC lesions)

Intervention type	Mean percent (95% CI)	Mean percent (95% CI)
Surgery/MMS (A,B)	88.8 (73.7, 95.7)	88.8 (44.3, 98.8)
Heat/cold (C)	60.5 (32.4, 83.0)	60.5 (12.7, 94.2)
Radiation (D)	79.1 (55.2, 92.1)	79.1 (26.8, 97.5)
PDT (E)	97.9 (93.1, 99.4)	97.9 (81.1, 99.8)
Drugs (F)	94.2 (37.5, 99.8)	94.2 (25.0, 99.9)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Observer-reported cosmetic outcomes, all BCC lesions

We describe only the results between intervention categories, because data are sparse for the comparison of individual observations. In total, 10 RCTs (1460 lesions) were included in this analysis.[45-48, 62, 66, 81, 94, 100] Nine RCTs were deemed to be at low or moderate risk of bias. The evidence graph in Figure 11 shows the observed comparisons based on RCTs that report observers' (investigators' or providers') assessments of "at least good" cosmetic outcome. The cosmetic outcome was assessed using different scales in each RCT, though often on scales of that included poor, fair, good, and excellent or similar. We provide analyses for an "at least good" cosmetic outcome. The evidence graph is sparsely connected. Details about the comparisons between these RCTs are in the box:

Studies (total sample)	10 (1460)
Total sample by intervention	(A,B): 426; (D): 113; (C): 109; (E): 443; (F): 354; (I,J): 15
Total sample by intervention, (min, max)	15, 443
Data by comparison	(A,B--D): 1 (244); (A,B--E): 2 (235); (A,B--F): 1 (344); (C--E): 4 (209); (E--F): 1 (370); (E--I,J): 1 (58)
Studies by comparison (min, max)	1, 4
Total sample by comparison (min, max)	58, 370
Followup median (min, max)	12 (12, 60) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Figure 11. Evidence graph of RCTs comparing observer-assessed cosmetic outcomes (all BCC lesions)

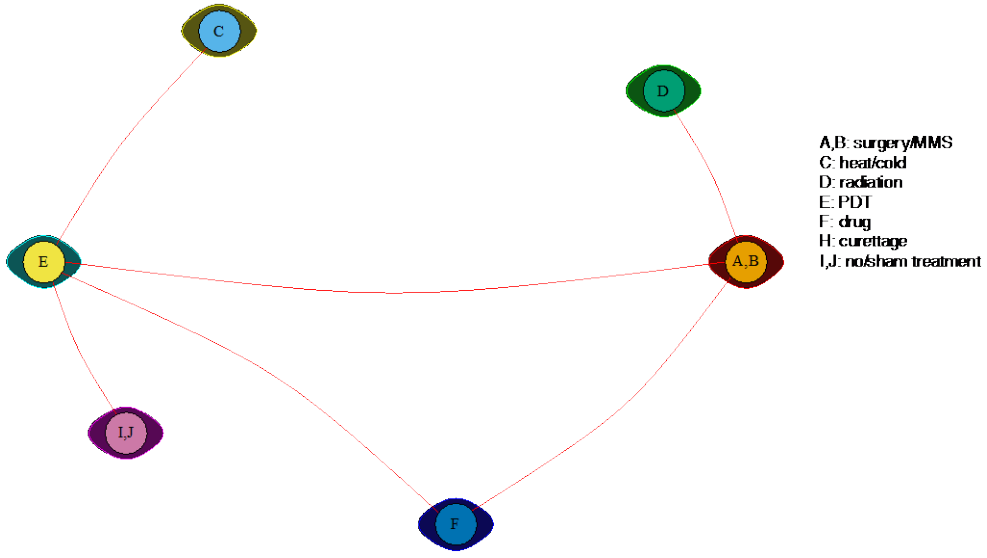


Table 40 has the results of the comparisons between intervention categories based on a network meta-analysis. Most comparisons are indirect (denoted by shaded cells) and have wide confidence intervals. For comparisons with head-to-head data (denoted by unshaded cells), the numbers in the table are very similar whether information from indirect comparisons is included

or excluded. Overall, the results are compatible with the corresponding results for patient-rated cosmetic outcomes. Specifically, four out of 15 comparisons are statistically significant: For example, based only on indirect data, surgical interventions (A,B) are favored over radiation (D), and based on direct and indirect data, PDT (E) is favored over surgical interventions (A,B).

Table 40. Relative odds ratios between intervention categories for at least good cosmetic outcome as assessed by an observer (all BCC lesions)

Surgery/MMS (A,B)	0.42 (0.12, 1.47)	3.57 (0.83, 15.36)	0.16 (0.06, 0.40)	0.38 (0.12, 1.18)	0.14 (0.01, 2.04)
2.37 (0.68, 8.25)	Heat/cold (C)	8.45 (1.42, 50.4)	0.37 (0.13, 1.06)	0.90 (0.22, 3.64)	0.33 (0.02, 5.11)
0.28 (0.07, 1.21)	0.12 (0.02, 0.71)	Radiation (D)	0.04 (0.01, 0.22)	0.11 (0.02, 0.61)	0.04 (<0.005, 0.76)
6.39 (2.5, 16.35)	2.70 (0.94, 7.74)	22.81 (4.56, 114.26)	PDT (E)	2.43 (0.81, 7.33)	0.89 (0.06, 12.23)
2.63 (0.85, 8.14)	1.11 (0.27, 4.48)	9.38 (1.63, 54.02)	0.41 (0.14, 1.24)	Drugs (F)	0.36 (0.02, 5.78)
7.22 (0.49, 106.52)	3.05 (0.2, 47.44)	25.76 (1.31, 505.2)	1.13 (0.08, 15.59)	2.75 (0.17, 43.61)	No/sham treatment (I,J)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Table 41 shows the average percentage of patients with at least good cosmetic outcomes in the RCTs, based on the same network meta-analysis as the Table above. The mean percentage of lesions with cosmetic outcome rated as good or excellent ranged between 74.3 and 89.8 percent for interventions that destroy the lesion with heat or cold (C), drugs (F), PDT (E) and no or sham treatment (I,J), and was 55.0 percent for surgical treatments (A,B). Radiation (D) had the smallest percentage of at least good cosmetic outcome. The confidence intervals for these proportions are wide. Refer to the previous Table for a pairwise comparison between these treatments.

Table 41. Mean fractions of lesions with at least good cosmetic outcome as assessed by an observer (all BCC lesions)

Intervention type	Mean fraction percent (95% CI)	Forecasted fraction percent
Surgery/MMS (A,B)	55.0 (34.7, 73.8)	55.0 (15.1, 89.3)
Heat/cold (C)	74.3 (51.5, 88.8)	74.3 (28.0, 95.6)
Radiation (D)	25.5 (7.1, 60.7)	25.5 (3.3, 77.3)
PDT (E)	88.7 (78.9, 94.2)	88.7 (54.2, 98.1)
Drugs (F)	76.3 (52.8, 90.2)	76.3 (29.6, 96.1)
No/sham treatment (I,J)	89.8 (40.1, 99.1)	89.8 (28.3, 99.5)

MMS= Mohs Micrographic Surgery; PDT=Photodynamic Therapy

Evidence from NRCSs

Three NRCS reported investigator-evaluated results for cosmetic outcomes.[139, 144, 147]

The first one compared surgical excision (A) and PDT with ALA (E2). It reported investigator-evaluated cosmetic outcomes in a matched population of 94 superficial (64%) and nodular (36%) BCCs in 74 patients at 12 months after treatment. The study was rated as having a moderate risk of bias due to lack of blinding and unclear reporting. The mean age was 66, with an age range of 49 to 90, 47 percent of the population was female. The group that received ALA-

PDT reported significantly better cosmetic results on a 4-level scale of poor to excellent (OR 10.2; 95% CI 4.0 to 26.1).[144]

A second NRCS reported whether an investigator saw pigmentation changes or alopecia in a small matched population of 40 patients treated with different doses of brachytherapy (36.6 versus 42 Gy). The risk of bias of this study was determined to be moderate, primarily for lack of blinding and unclear reporting of baselines. The mean age was 75, 45 percent were female, and all had a Fitzpatrick skin score of I (47.5%) or II (52.5%). Forty-five percent of the BCCs were superficial, while 55 percent were nodular; 75 percent were on the head and neck and 25 percent on the trunk or extremities. The lower dose had one fewer patient with pigmentation changes or alopecia (OR 0.81, 95% CI 0.23 to 2.86), but this difference was not significant.[139]

The third NRCS reported investigator-evaluated results for cosmetic outcomes to a median of 31.8 months after treatment, with two different doses and schedules of orthovoltage radiotherapy. The risk of bias was determined to be low with well-balanced arms, outcome assessors blinded, and full followup. The population consisted of 436 lesions in 385 elderly people, with BCCs (71%) and SCCs (29%). The mean age was 78, and 42 percent were female. A lower dose of radiation (37 Gy) had a slightly better cosmetic outcomes on a 4-level scale of poor to excellent than the higher dose (45 Gy), but this difference was not significant (RR: 1.048, 95% CI0.170 to 6.473).[147]

Quality of life, all BCC lesions

One RCT[61] and one NRCS[138, 140-143] reported eligible results. The former informs on the comparison between surgical excision (A) and MMS (B), and the latter on the comparison between excision (A), MMS (B), and electrodessication and curettage (C3).

Evidence from RCTs

The RCT reported on both quality of life and anxiety in a population of 408 primary BCCs (BCC) in 374 people, randomized to surgical excision (A; n=204) or MMS (B; n=204). The mean age of patients was 67.7. The majority of tumors were located in the H-zone (93%) with the highest distribution in the frontal/temporal area (31%). Approximately half of all lesions had an aggressive histological subtype (47% BCC). Differences in tumor location or subtype were not significantly different between treatment groups. The Quality of life (emotional reactions, energy, pain, sleep, social isolation, and physical mobility) and level of anxiety of patients were measured at baseline and 6 months post-treatment, using the Nottingham Health Profile and the State-trait Anxiety Inventory, respectively. Both questionnaires were administered by a single researcher, and only patients with a single BCC were evaluated for these outcomes. At baseline and 6 months post-treatment, patients in both treatment groups showed good "health-related quality life" and a "minimum level of anxiety," with no observable statistically significant differences between the two groups for any measure.[61]

Evidence from NRCSs

The NRCS reported skin-specific quality of life in three domains: symptoms, emotion, and functioning in 1174 patients with 1488 lesions in a Veterans Affairs clinic. This study was deemed to have a low risk of bias, with balanced groups, consecutive recruitment, blinding of outcome assessors, and adequate accounting for people lost to followup. Most (75%) of the lesions were BCCs; the other 25 percent were SCCs; 26 percent were female, 40 percent had a Fitzpatrick skin score of I or II, and 3 percent were immunocompromised due to prior solid-organ transplant. The lesions were treated by MMS (B; n=246; 65% in H-zone of the face), surgical excision (A; n=251; 26% in H-zone of the face), and electrodessication and curettage (ED&C) (C3; n=136; 11% in H-zone of the face).[138, 140-143]

Table 42 shows the propensity-matched net differences between arms for improvement from baseline for each of the three reported Skindex domains (symptoms, emotions, and function). The authors used a shortened version of the Skindex, which they had previously validated in a similar population.[152] The Skindex has a total of eight domains (cognitive effects, social effects, depression, fear, embarrassment, anger, physical discomfort, and physical limitations) each on a scale from 0 (no effect) to 100 (maximum effect).[153]

The unadjusted results in a large population showed large and significant differences, primarily in favor of Mohs and surgical excision as compared to ED&C, but also favoring Mohs over excision, particularly for the domains of emotions and functioning. However, these results are subject to residual confounding. The propensity-matched results include a smaller population, and thus, while they show potentially large differences, the differences cannot be distinguished from chance.[138, 140-143]

Table 42. Quality of Life measured with Skindex

Outcome	Arm	N/arm	Baseline score	comparison	Net Difference at 2 years	N propensity-matched pairs
QoL: Skindex Symptoms	ED&C	136	19.6 (23.6)	excision vs ED&C	-1.6 (-9.8, 6.7)	51
	excision	251	21.7 (23.2)	Mohs vs ED&C	9.2 (-2.1, 20.5)	24
	Mohs	246	21.8 (23.5)	Mohs vs excision	4.0 (-3.1, 11.1)	81
QoL: Skindex Emotions	ED&C	136	33.0 (28.0)	excision vs ED&C	13.2 (3.3, 23.1)	51
	excision	251	38.9 (30.4)	Mohs vs ED&C	23.6 (10.1, 37.2)	24
	Mohs	246	46.3 (27.0)	Mohs vs excision	3.4 (-3.8, 10.7)	81
QoL: Skindex Functioning	ED&C	136	12.1 (21.7)	excision vs ED&C	3.1 (-3.5, 9.8)	51
	excision	251	15.1 (24.6)	Mohs vs ED&C	3.7 (-4.6, 12.0)	24
	Mohs	246	14.0 (21.1)	Mohs vs excision	4.2 (-2.3, 10.8)	81

ED&C= electrodessication and curettage; QoL=Quality of Life

Mental health, all BCC lesions

A single RCT reported information on anxiety measured with the State-Trait Anxiety Inventory at 6 months, for a population of 408 primary BCCs (BCC) in 374 people randomized to surgical excision (A; n=204) or MMS (B; n=204). No statistically significant differences were found between the comparators. This RCT is summarized in some more detail in the Quality of Life section, under Evidence from RCTs.[61]

Patient satisfaction, all BCC lesions

We did not identify eligible RCTs with results for this outcome.

Mortality, all BCC lesions

Three RCTs[21, 45, 77, 81, 83, 84] and 1 NRCS[147] reported results on all cause mortality.

Evidence from RCTs

The first RCT reported mortality between 1 and 3 years in 501 people with 1 superficial BCC lesion each for the comparison of PDT with MAL (E1), 5-FU (F1), and imiquimod (F2). The risk of bias for this study was low, with randomization and allocation concealment adequately reported, blinding of outcome assessors, high similarity of groups at baseline, and low loss to followup. The median age was 63 (range 26 to 91), 49 percent were women, and most lesions were on the trunk (60%), extremities (27%), and face excluding the H-zone (13%). All-cause mortality was recorded for 5 of 196 (2.6%) patients in the PDT with MAL (E1) arm, 2 of 198 (1.0%) in the 5-FU arm (F1), and 4 of 189 (2.1%) in the imiquimod arm (F2).[45, 83, 84]

The second RCT compared surgical excision (A) (n=49) to PDT with MAL (E1) (n=52). The average age was 68 (range 38 to 95), and 40 percent were female. Most (88%) had Fitzpatrick skin types II (46.5%) and III (41.5%). The risk of bias for this study was judged to be relatively high because the groups were not similar at baseline, there was no blinding, and there was a high loss to followup after a year. Mortality at 1 and 2 years was not statistically significantly different in the excision (2/46, 4.3%) and MAL-PDT groups (2/50, 4.0%).[21, 81]

The third RCT compared surgical excision (A) without intraoperative evaluation of the excised margins (n=199) versus MMS (B) (n=198). It reported results for long-term mortality in people with unspecified BCCs on the face, about half of which were classified as an "aggressive histological subtype" between 18 months and 5 years. The average age was 68 (SD 12), and 39.7 percent were female. The average lesion size was 1.28 cm^2 (SD 1.36) in the MMS arm and 1.77 cm^2 (SD 1.28) in the surgical excision arm. The risk of bias was judged to be moderate to high because of lack of baseline details given, lack of blinding, and high loss to followup. Thirty-six (18%) died in the MMS arm as compared to 34 (17%) in the excision arm. None of the deaths were deemed to be related to the tumor or the treatment.[77]

Evidence from NRCSs

One NRCS reported results for long-term mortality, from 12 to a median of 31.8 months after treatment with two doses of external radiation (orthovoltage range) therapy. It was deemed that there was low risk of confounding or measurement bias based on the fact that arms were well-

balanced, outcome assessors were blinded, and no patients were lost to followup. The population consisted of 436 lesions in 385 elderly people, with BCCs (71%) and SCCs (29%). The mean age was 78, and 42 percent were female. The 45 Gy dose of radiation had a lower mortality (16.1%) than the 37 Gy dose group (30.5%), but the mean age in the lower dose group was significantly higher (81.3 vs. 73.3 years). Once adjusted for age, number of lesions per patient, histology, severity, and lesion site, the difference in mortality was not significant (Adjusted HR: 0.662; 95% CI 0.387 to 1.131).[147]

Costs and resource use, all BCC lesions

No RCTs informed on U.S. costs or on use of resources.

One NRCS reported cost and resource use outcomes in patients.[151] It compared surgical excision (A), MMS (B), and electrodessication and curettage (C3). Among the 936 examined lesions, 80 percent (n=748) were BCC and 20 percent (n=188) were SCCs. The risk of confounding bias of this study was determined to be low with differences at baseline controlled for in multivariate analysis, and no loss to followup. Females accounted for 59.4 percent of the population. Overall, 60.1 percent (n=563) of tumors in the study sample presented on the head and neck. Of these, the majority (56.3%) was treated by MMS; the majority (69.3%) of tumors presenting on the trunk and extremities were treated with electrodessication and curettage (ED&C). Similarly, 31.5% (295) of tumors presented in the H-zone, with the majority (80%) of these treated with MMS, compared to a majority (36.8% and 36.2%) of tumors not in the H-zone treated with ED&C and surgical excision, respectively. Differences in histology of the tumors and tumor diameter across treatment types were not observed to be statistically significant.

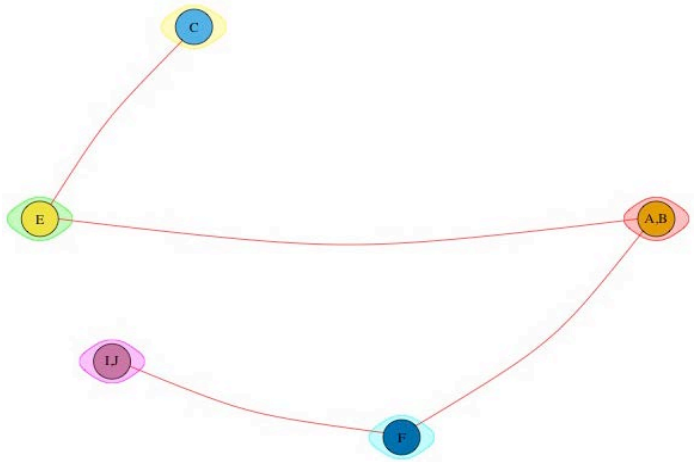
In both adjusted and unadjusted analyses of total surgical care, there was a statistically significant difference ($p<0.001$) in costs by treatment type. MMS treatments were observed to have the highest primary procedure and follow-up visit costs compared to excision (by, on average, $857 in adjusted analyses). Excision had the second highest costs for both primary procedure and follow-up visit, and ED&C had the lowest. Also, in both adjusted and unadjusted analyses, total fees for all surgical care were significantly higher for large tumors (>10 mm) and for H-zone locations. Independent predictors of higher total costs were determined using multivariate regression log models and included presentation of tumor at the head or neck, greater than 10mm lesion diameter, and repair with flap or graft. However, the study did not take fees related to recurrence into account.[151]

Adverse events, all BCC lesions

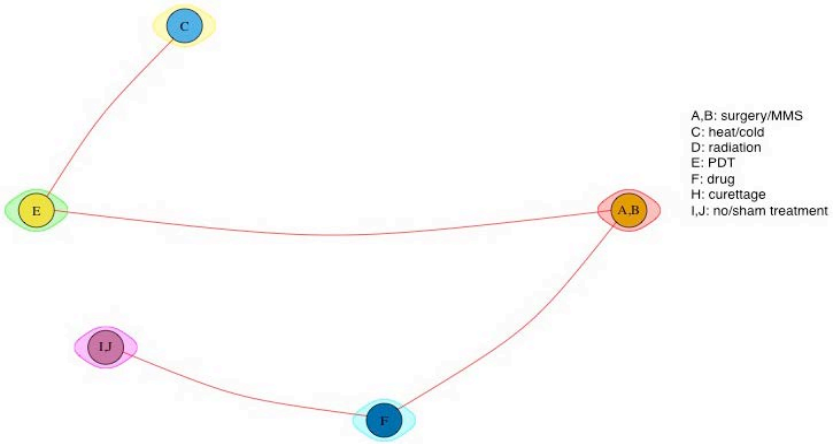
In this section we describe only results between intervention categories, because data are sparse for the comparison of individual observations. Figure 12 shows the evidence graph for the comparison of the frequency of adverse events leading to discontinuation, serious adverse events, pain after treatment completion, and infection of the treated site. Reporting of adverse events was not consistent across RCTs. The Appendix enumerates other types of adverse events that were reported.

Figure 12. Evidence graph of RCTs comparing frequency of adverse events (all BCC lesions)

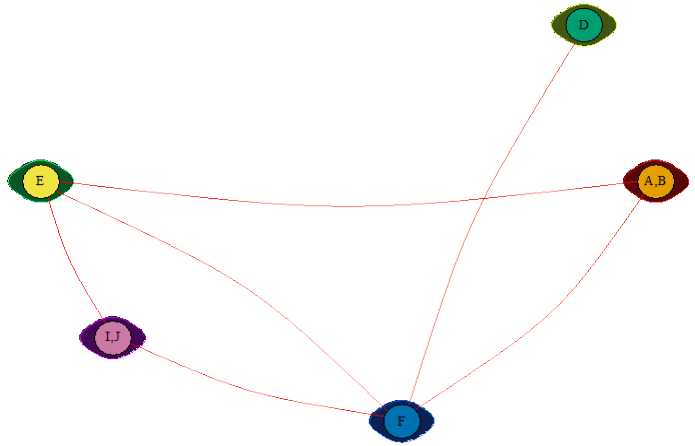
(A) Leading to treatment discontinuation



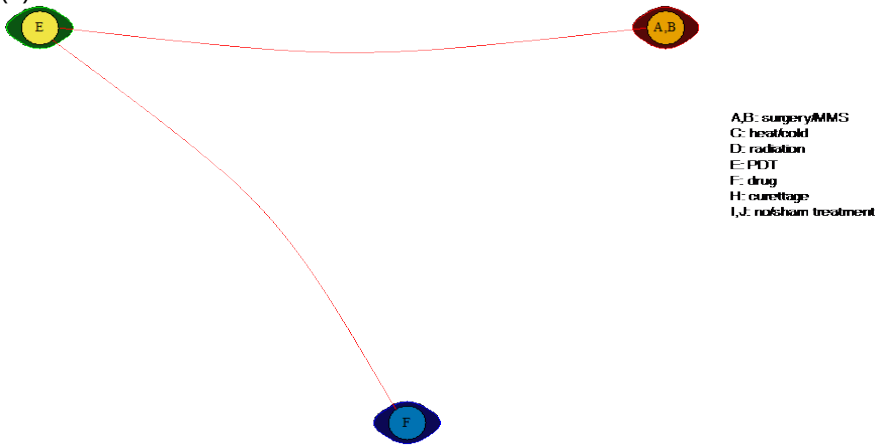
(B) Serious adverse events



(C) Pain (after treatment completion)



(D) Infection of the treated site



The evidence graphs in Figure 12 are sparsely connected. For parsimony, we do not report relative effects for comparisons of the frequency of each type of adverse event. The box has details about the comparisons by type of adverse event.

	Adverse events leading to treatment discontinuation[47, 48, 51, 64, 81, 88, 90]	Serious adverse events[19, 45, 48, 51, 54, 90, 94]	Pain after treatment[45, 48, 50, 51, 62, 63, 65, 81, 89, 90, 94]	Infection of treated site[45, 81, 94]
Studies (total sample)	7 (1733)	7 (1395)	11 (1612)	3 (682)
Total sample by intervention	(A,B): 287; (E): 120; (F): 782; (I,J): 486; (C): 58	(A,B): 413; (E): 397; (F): 523; (I,J): 44; (C): 18	(D): 12; (F): 705; (I,J): 176; (E): 368; (A,B): 351	(E): 348; (F): 189; (A,B): 145
Total sample by intervention, (min, max)	58, 782	18, 523	12, 705	145, 348
Data by comparison	(A,B--E): 1 (118); (A,B--F): 1 (483); (E--C): 1 (118); (F--I,J): 4 (1014)	(A,B--E): 2 (369); (A,B--F): 1 (483); (E--F): 1 (385); (E--C): 1 (34); (F--I,J): 2 (124)	(D--F): 1 (27); (F--I,J): 5 (379); (F--E): 1 (339); (F--A,B): 1 (439); (I,J--E): 1 (131); (E--A,B): 2 (297)	(E--F): 1 (385); (E--A,B): 2 (297)
Studies by comparison (min, max)	1, 4	1, 2	1, 5	1, 2
Total sample by comparison (min, max)	118, 1014	34, 483	27, 439	297, 385
Followup median (min, max)	[during treatment]	12 (1, 60) months	3 (0.5, 12) months	3 (1, 12) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

We report mean fractions of adverse events per intervention catgory, based on a joint analysis of all RCTs reporting the same outcome. Most likely, adverse events were defined differently across studies, but these definitions were often not clearly described. Results for adverse events, as defined by each study, are in Table 43 and come from different analyses.

Drugs had the highest frequency of adverse events leading to treatment discontinuation was (4.9%; 95% CI, 2.0 to 20.1); for other interventions, it was less than 1.2 percent. Surgical interventions and PDT are one-time procedures and cannot be “discontinued”; for parsimony of exposition, however, in the descriptive analyses in Table 43 we assigned 0 discontinuation events to these interventions.

The frequency of adverse events characterized as “serious” by the investigators was smaller than 3.6 percent for all intervention categories.

Pain after treatment was most commonly encountered for surgical interventions (21.5%) and for PDT (20.7%), and was least common with sham treatments (2.9%).

Infections at the treatment site were described in 5.5 percent of lesions with surgical treatments (95% CI 28 to 10.7), and were reported in less than 1 percent for PDT (E) and drugs (F). No information on infections was available for treatments that destroy lesions with heat or cold (C) or for no (or sham) treatment.

Table 43. Mean fractions of adverse events, using each RCT's definitions (all BCC lesions)

Intervention type	(A) Leading to discontinuation		(B) Serious*	(C) Pain after treatment		(D) Infection of the treated site*
	Mean	Forecast	Mean	Mean	Forecast	Mean
Surgery/MMS (A,B)	Not defined**	Not defined**	0.6 (0.2, 2.4)	21.5 (8.1, 46.2)	21.5 (1.7, 81.5)	5.5 (2.8, 10.7)
Heat/cold (C)	0.9 (0.0, 20.1)	0.9 (0.0, 29.0)	2.6 (0.2, 31.0)	12.9 (0.8, 73.1)	12.9 (0.3, 87.5)	NA
PDT (E)	Not defined**	Not defined**	0.7 (0.2, 2.7)	20.7 (8.2, 43.3)	20.7 (1.6, 80.3)	0.5 (0.1, 2.4)
Drugs (F)	4.9 (2.0, 11.6)	4.9 (0.6, 29.2)	3.6 (2.0, 6.5)	9.9 (4.4, 20.9)	9.9 (0.7, 61.6)	0.5 (0.1, 3.7)
No/sham treatment (I,J)	1.0 (0.2, 4.4)	1.0 (0.1, 9.8)	2.4 (0.3, 15.2)	2.9 (0.9, 9.4)	2.9 (0.2, 33.5)	NA

* No forecasts for these outcomes (fixed effects analyses only); NA: not applicable. ** Surgical interventions and PDT are one-time procedures and cannot be "discontinued"; for parsimony of exposition, however, in the descriptive analyses in the Table we assigned 0 discontinuation events to these interventions. MMM=Mohs micrographic surgery; PDT=photodynamic therapy

Evidence from NRCSs

Results on the frequency of adverse events are reported in three NRCSs.[147, 149, 150]

The first NRCS reported on adverse events in 12 patients with 1 superficial BCC each. The mean lesion area was 52 mm^2, and the lesions were located on the trunk or neck (67%) or forearm (33%). This study was deemed to have high risk of confounding bias, because of baseline imbalance. The mean age was 61 (range 52 to 78), and 33% were female. Six lesions were treated with imiquimod (F2) and six with a vehicle (J). More people in the vehicle arm (3 of 6) reported application site adverse events than in the imiquimod arm (2 of 6) during treatment, both erythemas.[150]

The second NRCS reported on adverse events in 74 patients with 1 nodular BCC each, receiving different doses of vismodegib (F5, other drug). It was deemed that this study was at moderate risk of confounding bias; it was not blinded, and it was not possible to assess for baseline (im)balance, because pertinent information was not reported. The lesion diameter ranged from 10 to 30 mm, and all were located in the scalp, head, neck, trunk or limbs. The mean age was 63.6 (SD 12; range 40 to 89), and 22 percent were female; 99 percent were white. Twenty-four lesions were treated with vismodegib for 12 weeks then were excised; twenty-five were treated with vismodegib for 12 weeks then had a 24-week observation period before excision; and 25 were treated with vismodegib for 16 weeks then were excised. Just about everyone (99%) reported at least one adverse event, including muscle spasms (76%), alopecia (58%), and changes in tasting, namely dysgeusia (50%) and ageusia (30%).[149]

The third NRCS reported results for any adverse events, from 12 to a median of 31.8 months after treatment with two doses of (orthovoltage) radiation therapy (D1). The risk of bias was determined to be low; arms were well-balanced at baseline, outcome assessors were blinded, and no patients were lost to followup. The lower-dose group (36 Gy) had fewer adverse events (5.9% as compared to 4.0% in the 45 Gy group), but no adjusted analysis was available for this outcome.[147]

Dose response analyses for drugs, all BCC lesions

Table 44 summarizes analyses from phase II or phase II/III trials on different doses or application schedules for drugs (F), stratified by whether the patients had superficial, nodular, or a mix of superficial and nodular BCC lesions in 16 studies.[44, 50, 57-59, 64, 65, 70, 72, 78, 89, 90, 93, 96, 97] Results cannot be combined across these studies in a straightforwardly interpretable way. Overall, the general pattern was that, with increasing intensity of treatment (higher doses or more applications) there was an apparent increase in the frequency of adverse events; but it is not always clearly reported whether this was statistically significant or not.

Special populations

No studies reported comparative results in special populations of interest, specifically patients at the end of life or immunocompromised patients.

Table 44. Summary of phase II or II/III trials comparing different doses or intensities of application schedules for drugs (all BCC lesions)

PMID Author	Arm1 (n)	Arm2 (n)	Arm3 (n)	Arm4 (n)	Arm5 (n)	Arm6 (n)	Arm7 (n)	Authors' conclusion
Superficial Lesions								
12196749 Geisse	Vehicle (32)	Imiquimod 5% 3x/wk (29)	Imiquimod 5% 5x/wk (26)	Imiquimod 5% 1x/day (31)	Imiquimod 5% 2x/day (10)			"There was a positive association between dosing frequency and complete response rate; higher response rates were associated with more frequent dosing…An acceptable safety profile was seen in 3 of the 4 imiquimod dosing regimens. Only the most frequent dosing regimen, twice daily for 12 weeks, presented a safety profile that was judged not acceptable because of severe local skin reactions at the treatment site."
15097956 Geisse	Vehicle 5x/wk (175)	Vehicle 7x/wk (171)	Imiquimod 5% 5x/wk (178)	Imiquimod 5% 7x/wk (170)				"The results from these Phase III studies confirm that imiquimod has higher complete clearance rates than vehicle cream for each of the active treatment groups. Additionally, there was not a statistically significant or clinically meaningful difference in complete clearance rate noted between the imiquimod 5/week and 7/week (73% composite and 79% histologic) treatment groups."
11312429 Marks	Imiquimod 5% 1x/day (33)	Imiquimod 5% 2x/day (3)	Imiquimod 5% 1x/day 3x/wk (33)	Imiquimod 5% 2x/day 3x/wk (30)				"There was a dose-response gradient varying from 3 of 3 (100%) in the twice-every-day regimen group to 23/33 (69.7%) in the once-daily 3 times/week regimen group…This study confirms previous work suggesting that imiquimod 5% cream is likely to be of value in the treatment of sBCC."
20546215 Siller	Vehicle (12)	Ingenol mebutate 0.0025% Days 1 and 2 (8)	Ingenol mebutate 0.01% Days 1 and 2 (8)	Ingenol mebutate 0.05% Days 1 and 2 (8)	Ingenol mebutate 0.0025 % Days 1 and 8 (8)	Ingenol mebutate 0.01% Days 1 and 8 (8)	Ingenol mebutate 0.05% Days 1 and 8 (8)	The study was not powered to detect differences in treatment concentration and schedule, but the clinical and histological response was more common in 0.05% 1&2 day application compared to other doses or 0.05% 1&8 day application.
12452875 Sterry	Imiquimod 5% 2x/wk without occlusion (24)	Imiquimod 5% 2x/wk with occlusion (21)	Imiquimod 5% 3x/wk without occlusion	Imiquimod 5% 3x/wk with occlusion				"The complete response rate increased as dosing frequency increased, both with and without occlusion. However, the only statistically significant difference in response rate was seen when comparing the 2 days per week with occlusion and 3 days per week with occlusion groups (P = 0.004)."
Nodular lesions								
17610993 Eigentler	Imiquimod 5% 3x/wk for 8 weeks (45)	Imiquimod 5% 3/wk for 12 weeks (45)						"There were no significant differences between the treatment arms with respect to efficacy and tolerability."
1430394	5-FU 7.5	5-FU 15 mg						"Application of Fisher's exact test showed no differences in response

PMID Author	Arm1 (n)	Arm2 (n)	Arm3 (n)	Arm4 (n)	Arm5 (n)	Arm6 (n)	Arm7 (n)	Authors' conclusion
Orenberg	mg							between the treatment groups."
12224977 Shumack 12 weeks	Vehicle (24)	Imiquimod 5% 1x/day 3x/wk (20)	Imiquimod 5% 1x/day 5x/wk (23)	Imiquimod 5% 1x/day 7x/wk (21)	Imiquimod 5% 2x/day 7x/wk			"An increase in the complete response rate was seen with increasing dosing frequency. This increase was statistically significant (P.001) based on the Cochran-Armitage test for trend (2-sided)."
12224977 Shumack 6 weeks	Imiquimod 5% 1x/day 3x/wk (32)	Imiquimod 5% 2x/day 3x/wk (31)	Imiquimod 5% 1x/day 7x/wk (35)	Imiquimod 5% 2x/day 7x/wk (1)				"The highest complete response rate was seen in the once-daily dosing group. No statistically significant dose-response trend was detected."
12452875 Sterry	Imiquimod 5% 2x/wk without occlusion (24)	Imiquimod 5% 2x/wk with occlusion (21)	Imiquimod 5% 3x/wk without occlusion	Imiquimod 5% 3x/wk with occlusion				"No significant differences of complete response rate were detected between the four treatment groups (P = 0.700)."
Mixed lesions								
8708151 Alpsoy	IFN alfa-2b (15)	IFN alfa-2a plus IFN alfa-2b (15)					Mixed	"IFN alfa provides a safe and effective treatment for nodular and superficial BCC…The effectiveness is not increased by combining IFN alfa-2a and 2b."
10570388 Beutner	Imiquimod 5% 2x/day (7)	Imiquimod 5% 1x/day (4)	Imiquimod 5% 3x/wk (4)	Imiquimod 5% 2x/wk (5)	Imiquimod 5% 1x/wk (4)		Mixed	"The response of BCC to imiquimod noted in this pilot study appears to be excellent."
2107219 Edwards	IFN gamma 900,000 IU (14)						Mixed	"Although 76% of our subjects had one or more side effects, these were generally minor and were not dose related. It is likely that higher doses of interferon gamma injected intralesionally into basal cell carcinomas would produce a higher, perhaps clinically important, cure rate but might not result in a significant increase in side effects."
2383027 Edwards	IFN alfa-2b 30 million IU 3x (32)						Mixed	"Side effects were similar for both single and repeated dosage groups, and were those common to interferon… Side effects were similar for both single and repeated dosage groups, and were those common to interferon."
8996264 Miller	5-FU 0.5 ml 1x/wk for 6 wk (21)	5-FU 1.0 ml 2x/wk for 3 wk (18)	5-FU 0.5 ml 2x/wk for 3 wk	5-FU 0.5 ml 2x/wk for 4 wk (21)	5-FU 0.5 ml 3x/wk for 2 wk (17)		Mixed	"The intralesional administration of 5-FU/epi gel proved to be safe and effective in treating nodular and superficial BCCs. All regimens appeared to work well and there were no statistically significant differences among them."

PMID Author	Arm1 (n)	Arm2 (n)	Arm3 (n)	Arm4 (n)	Arm5 (n)	Arm6 (n)	Arm7 (n)	Authors' conclusion
			(19)					
15606733 Torres	Mohs plus Imiquimod 5% 5x/wk for 2 wk (12)	Mohs plus Imiquimod 5% 5x/wk for 4 wk (12)	Mohs plus Imiquimod 5% 5x/wk for 6 wk (12)				Mixed	"The application of 5% imiquimod cream before excision with Mohs micrographic surgery significantly reduced the size of the target tumor and resulted in a smaller surgical defect from the Mohs micrographic surgery excision (compared to vehicle groups)…the study was not designed and the sample sizes were not large enough to adequately characterize an imiquimod dose–duration response curve."
22511036 Tran	PDL 15 J/cm^2 (7)	PDL 7.5 J/cm^2 (7)					Mixed	Neither dose was statistically significantly different from the control group. "The results of our pilot study suggest that BCCs and SCCIS can be cleared in a single treatment using a pulsed-laser in a stacked pulse setting. However, given the small sample size of this pilot study, further larger scale studies will be needed to determine statistical significance and long-term recurrence rate and to further validate these findings."

Squamous Cell Carcinoma (SCC)

The evidence graph in Figures 13 and 14 depict eight comparisons between 10 interventions organized in four intervention categories. Comparisons between individual interventions are sparse, suggesting that limited, if any, conclusions can be drawn about which individual treatment is best for each outcome. Figure 13 has two connected subgraphs. The smallest one compares a laser-based preparation of the lesion for PDT treatment (C5+E2) versus PDT alone (E2), and the other comprises all other treatments. Information on each comparison is provided by at most three RCTs, and for most comparisons, by a single RCT.

The evidence is sparser when one considers the information that is actually available for specific outcomes. Figure 15 shows the corresponding evidence graphs for the outcomes for which we have the most data, namely recurrence, lack of histologic clearance, and lack of clinical clearance. RCT data exists for only 7, 4, and 8 of the 28 interventions, respectively. Evidence on other outcomes (quality of life, cosmetic outcomes, costs or resource use) is even sparser.

We identified one NRCS comparing curettage (H) versus cryotherapy (C1) in patients with SCC lesions. This study is described separately.[137]

Figure 13. Evidence graph depicting compared treatments in RCTs of SCC lesions

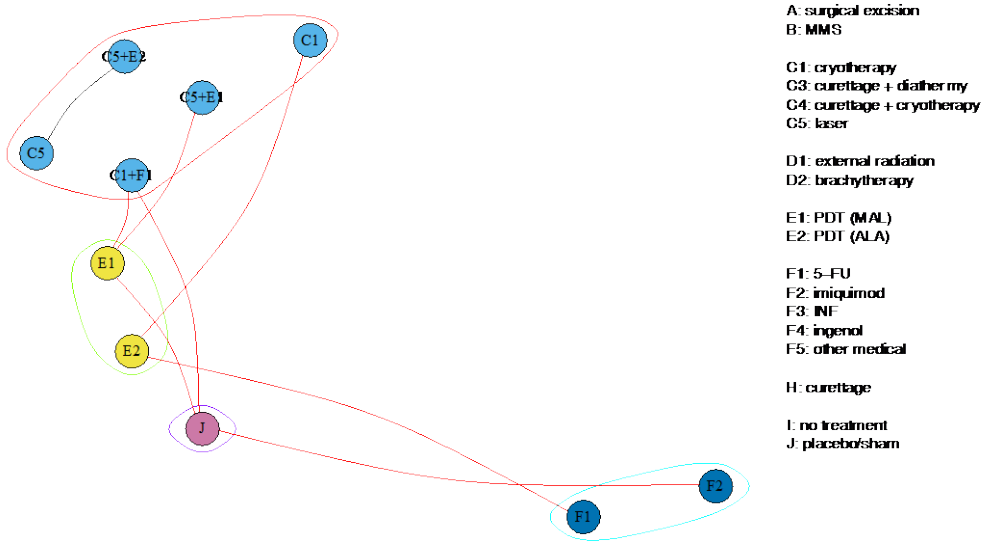
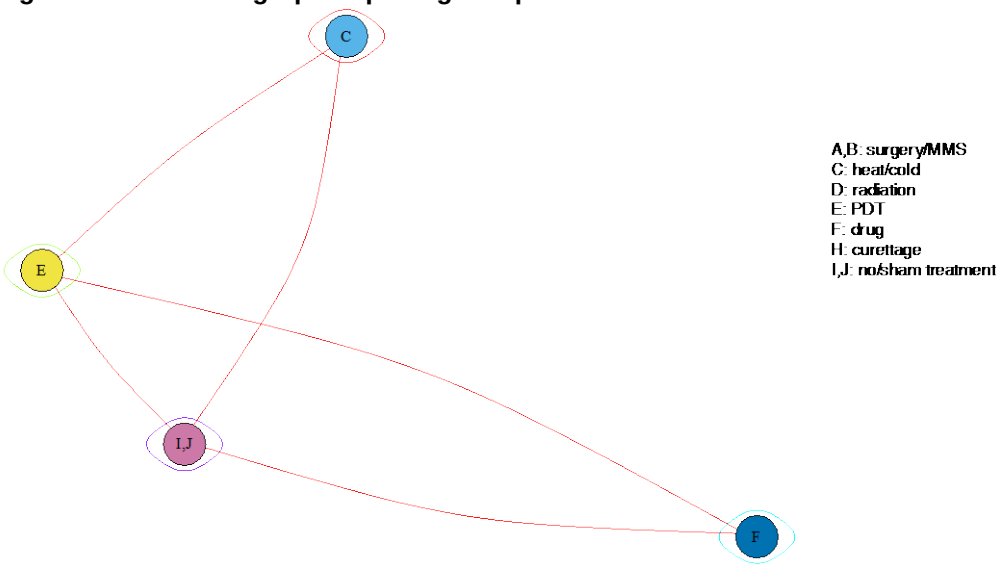


Figure 14. Evidence graph depicting compared treatments in RCTs of SCC lesions



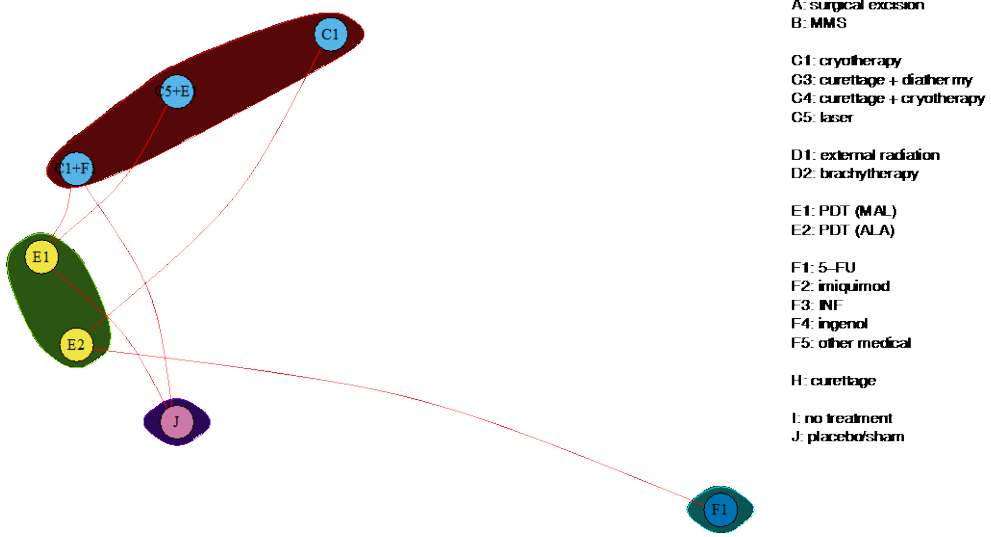
The characteristics of the six included RCTs are summarized in the Table 45. All RCTS included only participants with SCC in situ (SCCIS).

Across all trials, the mean or median age of enrollees ranged between 68.9 and 76 (median 74, 25th-75th percentile: 72.4 to 76). The proportion of female patients ranged between 40 and 87.5 percent (median 62.8, 25th-75th percentile: 54 to 80). When reported, the mean or median lesion area was between 82 and 429 mm^2, and the maximum diameter was between 18.9 and 26.2 mm. The majority of RCTs included lesions in various body locations, and only a few reported results stratified by lesion location (discussed separately). Based on this information, the RCTs included patients and lesions are typically encountered in clinical practice. No RCT focused on patients who were immunocompromised or had substantially limited life expectancy.

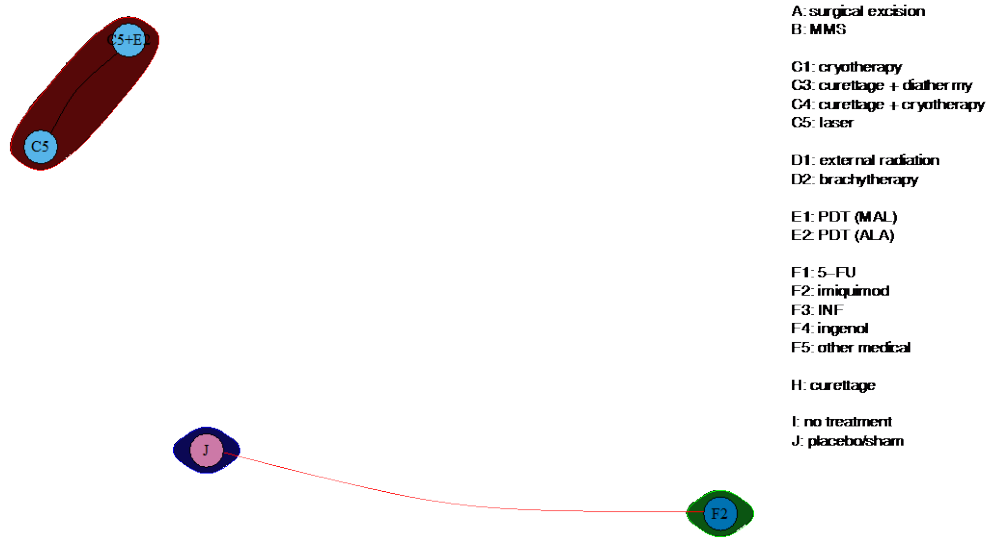
In terms of design characteristics, five RCTs had two arms and one had three arms. Analyzed sample sizes ranged between 18 and 209 (median=23.5, 25th-75th percentile: 18.25 to 37); sample sizes per RCT arm ranged between 11 and 91. Based on what was reported in the RCTs, we deemed that the allocation sequence was randomized using formal methods in one and successfully concealed in two RCTs, and that patients, providers, and outcome assessors were successfully blinded to the received treatments in one, two, and three RCTs, respectively. Our consensus assessment of the reported baseline characteristics across the compared arms in each RCT was that half of the RCTs (n=3) had arms that were likely balanced at baseline. In four RCTs fewer than 20 percent of patients had missing outcomes for any eligible outcome in any arm.

Figure 15. Evidence graphs for recurrence, histologic clearance, and clinical clearance for RCTs of SCC lesions

(A) Recurrence



(B) Lack of histologic clearance



(C) Lack of clinical clearance

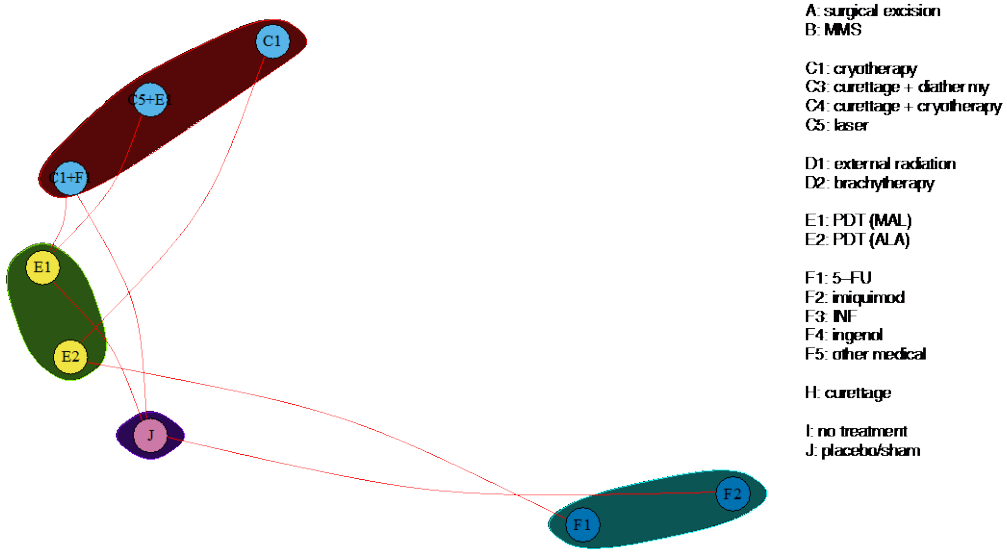


Table 45. Characteristics of studies of SCCIS populations.

Study	Arm	Age, mean	female %	Lesion size, mean	Lesion location (%)	1* Adequate randomization	2* Allocation concealment	3* Arms similar at baseline	4* Patients blinded	5* Providers blinded	6* Outcome assessors blinded	7* <20% loss to followup
Cai 2015 25899562	ALA-PDT + CO2 Laser	NR	50	2.62 cm	NR	Unsure	Yes	Yes	Unsure	Yes	Yes	Yes
	CO2 Laser	NR	62.5	2.58 cm	NR							
Ko 2014 24102369	Er:YAG AFL PDT	68.9	52.4	NR	extremities (100)	Unsure	No	Yes	No	Unsure	Yes	Yes
	MAL-PDT	68.9	52.4	NR	extremities (100)							
Morton 1996 8977678	cryotherapy	76	84	82 mm^2	hands (5), face (15), legs (80)	No	No	Yes	No	No	No	No
	ALA-PDT	76	84	150 mm^2	hands (5), face (10), legs (85)							
Morton 2006 16785375	MAL PDT	71.9	62	18.9 mm	face/scalp (23), extremities (65), trunk/neck (12)	No	No	Unsure	No	No	No	Yes
	PDT placebo	73.4	65	19.3 mm	face/scalp (25), extremities (67), trunk/neck (8)							
	Cryotherapy	74	59	19.4 mm	face/scalp (29), extremities (57), trunk/neck (14)							
	Fluorouracil	72.5	63	20.9 mm	face/scalp (19), extremities (69), trunk/neck (11)							
Patel 2006 16713457	imiquimod 5%	74	40	429 mm^2	NR	Yes	Yes	No	Yes	Yes	Yes	No
	vehicle	74	87.5	248 mm^2	NR							
Salim 2003 12653747	PDT	76	80	NR	extremities (100)	No	No	No	No	No	No	Yes
	5-FU	76	80	NR	face (12), extremities (88)							

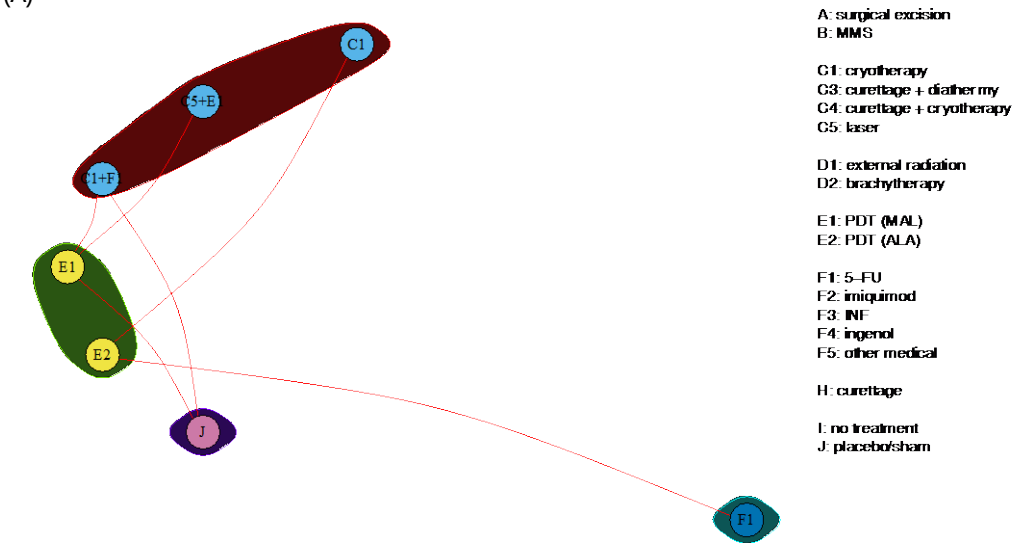
*Design items: 1: Adequate generation of a randomized sequence reported; 2: Adequate allocation concealment reported; 3: Group similarity at baseline; 4: Adequate blinding of patients reported; 5: Adequate blinding of providers reported; 6: Adequate blinding of outcome assessors reported; 7: Less than 20% missing for any eligible outcome in any arm. PDT=photodynamic therapy.

Recurrence, SCCIS lesions

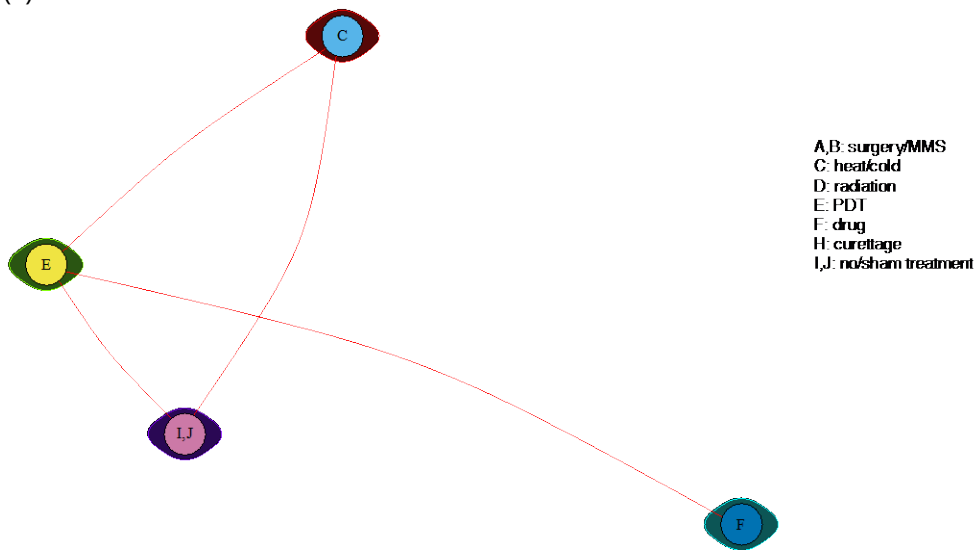
The evidence graph for recurrence with respect to individual treatments is sparse (Figure 15 [A] – reproduced in Figure 16 [A] for ease of reference). Detailed results at the RCT-level are in the Appendix.

Figure 16: Evidence graph of RCTs evaluating recurrence in SCCIS across (A) individual interventions and types of interventions (B).

(A)



(B)



Comparisons across intervention categories

In total, 4 RCTs (348 lesions) were included in this analysis.[68, 75, 76, 85] Two RCTs were deemed to be at low or moderate risk of bias. The comparisons are described in the box below.

Studies (total sample)	4 (348)
Total sample by intervention	(C): 136; (E): 175; (F): 33; (I,J): 4
Total sample by intervention, (min, max)	4, 175
Data by comparison	(C--E): 3 (278); (C--I,J): 1 (101); (E--F): 1 (66); (E--I,J): 1 (107)
Studies by comparison (min, max)	1, 3
Total sample by comparison (min, max)	66, 278
Followup median (min, max)	12 (12, 24) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Table 46 shows the relative odds ratios for recurrence across intervention categories. Based on direct data, the odds ratio for recurrence is not statistically significantly different between interventions that destroy the lesions with heat or cold (C) and PDT (E); however, the confidence interval does not exclude differences in the odds as large as 50 percent in either direction. Based on direct data, the odds ratio between PDT (E) and drugs (F) is statistically significant, favoring PDT.

In the Table, shaded cells correspond to comparisons that have been inferred from the analysis model, but that have not been examined in the included RCTs. For example, comparisons of drugs (F) and interventions that destroy the lesion with heat or cold (E) are indirect, and have very wide confidence intervals. For all comparisons that are empirically observed (all non-shaded cells in the Table), results using only head-to-head data agree well with the results from the network meta-analysis in Table 46.

Table 46. Relative odds ratios for recurrence between intervention categories (SCCIS lesions)

Heat/cold (C)	0.83 (0.33, 2.06)	0.17 (0.05, 0.55)	0.18 (0.02, 1.59)
1.21 (0.49, 3.01)	PDT (E)	0.20 (0.07, 0.62)	0.22 (0.03, 1.86)
5.96 (1.81, 19.61)	4.93 (1.6, 15.15)	Drugs (F)	1.06 (0.11, 10.44)
5.61 (0.63, 50.1)	4.64 (0.54, 39.96)	0.94 (0.1, 9.25)	No/sham treatment (I,J)

PDT=photodynamic therapy

Table 47 offers complementary information from the same analysis. For each intervention category, it shows the mean recurrence rate across the included RCTs. Interventions that destroy the lesion with heat or cold (C) and PDT (E) had on average lower recurrence rates (15.1% and 17.7%, respectively) compared to the other treatments. These estimates describe the outcome rates in the RCT arms, and are based on the relative effects in 46 and the observed baseline rates in the RCTs. Of note, the recurrence rate for drugs is 51.5 percent (95% CI 28.9 to 73.5), reflecting the high recurrence rates observed in the single RCT comparing 5-FU with PDT (ALA) in this analysis.

Table 47. Mean recurrence rates by intervention category (SCCIS lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
Heat/cold (C)	15.1 (8.1, 26.5)	15.1 (6.3, 32.1)
PDT (E)	17.7 (10.8, 27.8)	17.7 (8.1, 34.4)
Drugs (F)	51.5 (28.9, 73.5)	51.5 (24.7, 77.5)
No/sham treatment (I,J)	50.0 (11.2, 88.8)	50.0 (10.1, 89.9)

PDT=photodynamic therapy

Comparisons across individual interventions

As is evident from Figure 16, there are two connected subgraphs for this outcome: a smaller one comprising the comparison among cryotherapy (C1), MAL with ALA (E2), and 5-FU (F1), and a larger one among PDT with MAL with and without laser preparation (E1 and C5+E1), cryotherapy with 5-FU (C1+F1), and placebo. In total, 4 RCTs (348 lesions) were included in these analyses, as summarized in the box:

	First subgraph[68, 75]	Second subgraph[76, 85]
Studies (total sample)	2 (242)	2 (106)
Total sample by intervention	(C5+E1): 19; (E1): 122; (C1+F1): 97; (J): 4	(C1): 20; (E2): 53; (F1): 33
Total sample by intervention, (min, max)	4, 122	20, 53
Data by comparison	(C5+E1--E1): 1 (38); (E1--C1+F1): 1 (200); (E1--J): 1 (107); (C1+F1--J): 1 (101)	(C1--E2): 1 (40); (E2--F1): 1 (66)
Studies by comparison (min, max)	1, 1	1, 1
Total sample by comparison (min, max)	38, 200	40, 66
Followup (min, max)	(12, 12) months	(12, 24) months

A: surgical excision, B: Mohs Micrographic Surgery; C1: cryotherapy; C3: diathermy and curettage; C4: cryotherapy and curettage; C5: laser; D1: external radiation; E1: MAL photodynamic therapy; E2: ALA photodynamic therapy; F1: 5-FU; F2: Imiquimod; F3: Interferon; F4: Ingenol; H: curettage; J placebo.

Table 48 shows the relative effects for both subgraphs. Because the comparisons across individual observations are sparse, however, the confidence intervals of the odds ratios for most indirect comparisons are very broad and cannot exclude very large differences between the compared interventions.

Table 49 shows, for each intervention, the mean recurrence rates across all RCTs; estimates for interventions in both subgraphs are listed in the Table. It was not possible to compare statistically the estimated recurrence rates between an intervention in the first subgraph (e.g., PDT with MAL [E1]) and the second subgraph (e.g., cryotherapy [C1]), because they come from disjoint analyses.

Table 48. Relative odds ratios for recurrence between individual interventions (SCCIS lesions)

Cryotherapy + 5-FU (C1+F1)	6.14 (0.48, 77.78)	1.12 (0.31, 3.96)	0.24 (0.02, 2.48)			
0.16 (0.01, 2.06)	Laser + PDT (MAL) (C5+E1)	0.18 (0.02, 1.95)	0.04 (<0.005, 0.94)			
0.9 (0.25, 3.18)	5.5 (0.51, 58.9)	PDT (MAL) (E1)	0.22 (0.02, 2.13)			
4.11 (0.4, 41.76)	25.2 (1.06, 598.92)	4.58 (0.47, 44.79)	Placebo/sham (J)			
				Cryotherapy (C1)	1.34 (0.06, 28.22)	0.19 (0.01, 5.5)
				0.75 (0.04, 15.75)	PDT (ALA) (E2)	0.14 (0.01, 1.55)
				5.27 (0.18, 153)	7.06 (0.65, 77.1)	5-FU (F1)

PDT=photodynamic therapy

Table 49. Mean and forecasted recurrence rates by intervention category (SCCIS lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
First subgraph		
Cryotherapy + 5-FU (C1+F1)	22.4 (8.0, 48.8)	22.4 (5.3, 60.0)
Laser + PDT (MAL) (C5+E1)	4.5 (0.5, 31.6)	4.5 (0.4, 37.6)
PDT (MAL) (E1)	20.5 (9.0, 40.3)	20.5 (5.5, 53.3)
Placebo/sham (J)	54.2 (11.2, 91.8)	54.2 (8.8, 93.6)
Second subgraph		
Cryotherapy (C1)	13.0 (1.1, 67.2)	13.0 (0.5, 82.5)
PDT (ALA) (E2)	10.1 (1.5, 45.3)	10.1 (0.5, 69.4)
5-FU (F1)	44.1 (7.5, 88.5)	44.1 (3.1, 95.1)

PDT=photodynamic therapy

Recurrence, other subgroup analyses (lesion location, lesion size)

Evidence from RCTS

Table 50 below shows results on subgroup analyses for a four-arm RCT.[73, 75] Neither lesion location nor size were associated with differences in the treatment effect beyond what is expected by chance.

Table 50. Subgroup analyses by lesion location and size: results for recurrence (SCCIS lesions)

Study	Comparison	Timepoint	Subgroup	n/N arm 1 vs. n/N arm 2 vs. n/N arm 3	OR (95% CI); P-Value Within	P- Value Between
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	12 months	lesion location: extremities	11/60 vs. 11/63 vs. 0/1	1.06 (0.42, 2.67); 0.70 (0.03, 18.23); 0.66 (0.03, 17.18); p=1.000	p=0.483
			lesion location: face/scalp	6/22 vs. 2/27 vs. 1/2	4.69 (0.84, 26.15); 0.38 (0.02, 7.00); 0.08 (0.00, 1.82); p=0.084	
			lesion location: neck/trunk	2/15 vs. 2/13 vs. 1/1	0.85 (0.10, 7.04); 0.06 (0.00, 1.99); 0.07 (0.00, 2.35); p=0.209	
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	12 months	lesion diameter: 5-14 mm	0/27 vs. 4/40 vs. 1/1	0.15 (0.01, 2.86); 0.01 (0.00, 0.43), 0.04 (0.00, 1.17); p=0.018	NA
			lesion diameter: 15-29 mm	15/55 vs. 5/43 vs. 1/3	2.85 (0.94, 8.61); 0.75 (0.06, 8.89); 0.26 (0.02, 3.46); p=0.093	
			lesion diameter: >= 30 mm	3/12 vs. 6/20 vs. 0/0	0.78 (0.15, 3.93); NA; p=1.000	

NA = not significant; PDT = photodynamic therapy

Evidence from NRCSs

One NRCS reported recurrence for 80 SCCIS lesions in 67 people, treated with either curettage (44 lesions) or cryotherapy (36 lesions). This study was deemed to be of high risk of bias, primarily for lack of reporting (baseline data and dropout numbers were not given by arm), but also for lack of blinding and for a high long-term dropout rate. The mean age was 74 (range: 46 to 89), and the mean lesion area was 336 mm^2 (range 30 to 1890 mm^2). Eighty-two percent were female, and the lesions were located on the extremities (84%), trunk (7.5%), and head/neck (8.5%). The cryotherapy arm had a significantly higher rate of recurrence up to 22 months than the curettage arm (OR 5.65; 95% CI 1.65 to 19.39).[137]

Lack of histological clearance, SCCIS lesions

The evidence graph for recurrence with respect to individual treatments is sparse (Figure 15 [B] – reproduced in Figure 17 for ease of reference). For this outcome, one RCT compared between laser ablation (C5) versus a combination of laser ablation and PDT with ALA (C5+E2), and one RCT compared 5-FU (F2) versus placebo (J). An analysis of comparisons between intervention categories is superfluous, in that it would include the same evidence as in the latter comparison of 5-FU (F2) versus placebo (J). The comparisons in the two RCTs (50 lesions) are described in the box.

	First subgraph[79]	Second subgraph[53]
Studies (total sample)	1 (28)	1 (22)
Total sample by intervention	(F2): 12; (J): 16	(C5): 11; (C5+E2): 11
Total sample by intervention, (min, max)	12, 16	11, 11
Data by comparison	(F2--J): 1 (28)	(C5--C5+E2): 1 (22)
Studies by comparison (min, max)	1, 1	1, 1
Total sample by comparison (min, max)	28, 28	22, 22
Followup	7 months	6 months

A: surgical excision, B: Mohs Micrographic Surgery; C1: cryotherapy; C3: diathermy and curettage; C4: cryotherapy and curettage; C5: laser; D1: external radiation; E1: MAL photodynamic therapy; E2: ALA photodynamic therapy; F1: 5-FU; F2: Imiquimod; F3: Interferon; F4: Ingenol; H: curettage; J placebo.

Figure 17: Evidence graph of RCTs evaluating lack of histological clearance in SCCIS lesions across individual interventions

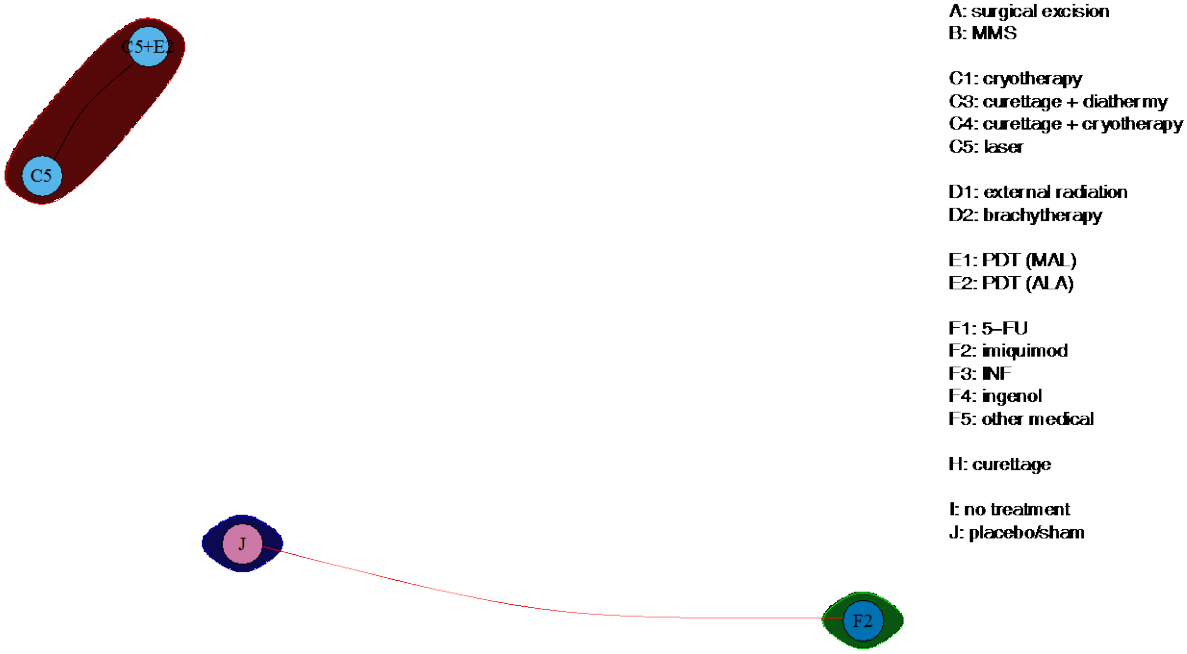


Table 51 shows the relative odds ratios for lack of histological clearance between individual interventions. Because of the very small sample sizes, the confidence intervals are very large. Table 52 has the respective fractions for lack of histological clearance in the two RCTs.

Table 51. Relative odds ratios for lack of histological clearance between individual interventions (SCCIS lesions)

(F1) 5-FU	0.01 (<0.005, 0.22)		
99 (4.45, 2202.23)	(J) placebo		
		(C5) laser	8.33 (0.78, 89.47)
		0.12 (0.01, 1.29)	(C5+E2) laser + PDT (ALA)

PDT=photodynamic therapy

Table 52. Mean lack of histological clearance (all SCCIS lesions).

Intervention type	Mean percent (95% CI)
First comparison	
5-FU (F1)	25.0 (8.3, 55.2)
Placebo (J)	97.1 (66.4, 99.8)
Second comparison	
Laser (C5)	45.5 (20.3, 73.2)
Laser with PDT (MAL) (C5+E2)	9.1 (1.3, 43.9)

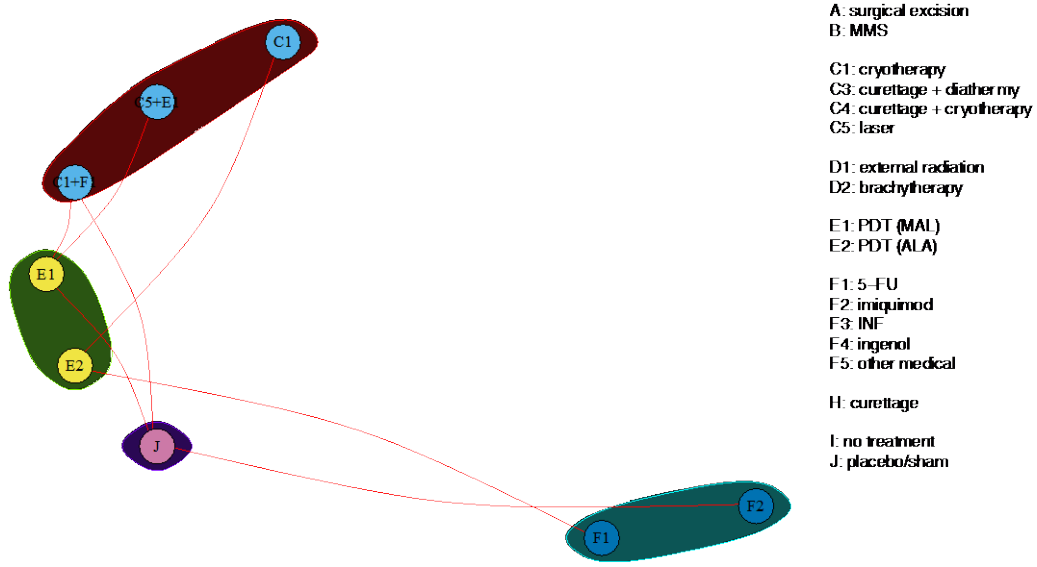
PDT=photodynamic therapy

Lack of clinical clearance, SCCIS lesions

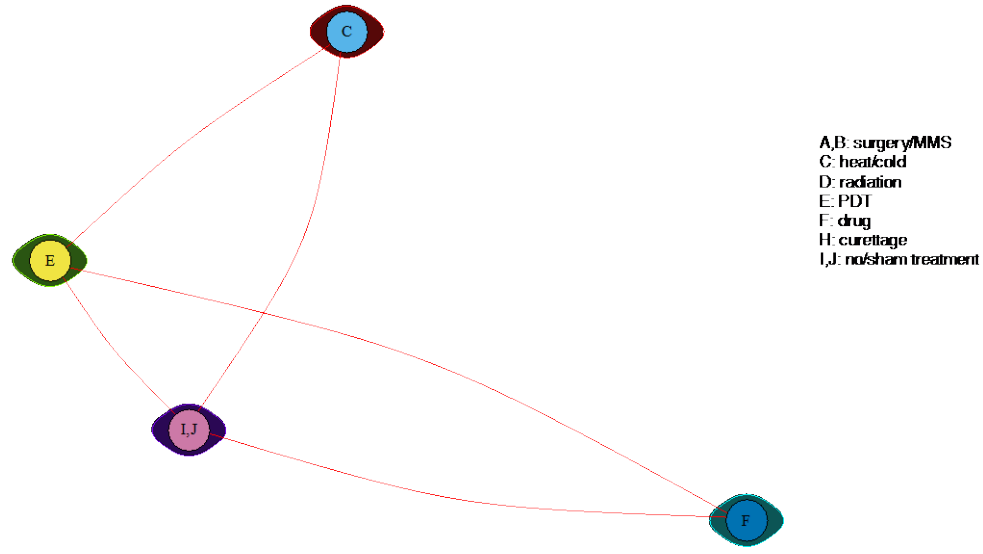
The evidence graph for recurrence with respect to individual treatments is sparse (Figure 15 [C] – reproduced in Figure 18 [A] for ease of reference). Detailed results at the RCT-level are in the Appendix.

Figure 18: Evidence graph of RCTs evaluating lack of clinical clearance in SCCIS lesions across (A) individual interventions and types of interventions (B).

(A)



(B)



Comparisons across intervention categories

In total, five RCTs (436 lesions) were included in this analysis.[68, 75, 76, 79, 85] Three RCTs were deemed to be at low or moderate risk of bias. The comparisons are described in the box.

Studies (total sample)	5 (436)
Total sample by intervention	(C): 166; (E): 190; (F): 45; (I,J): 35
Total sample by intervention, (min, max)	35, 190
Data by comparison	(C--E): 3 (323); (C--I,J): 1 (133); (E--F): 1 (66); (E--I,J): 1 (130); (F--I,J): 1 (28)
Studies by comparison (min, max)	1, 3
Total sample by comparison (min, max)	28, 323
Followup median (min, max)	3 (2, 12) months

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

Table 53 shows the relative odds ratios for clinical clearance across intervention categories. There were no statistically significant differences between the active interventions, although the confidence intervals for the odds ratios were wide and could not exclude large differences in the odds of the outcome in either direction. Nevertheless, all active interventions were favored beyond chance versus placebo.

Table 53. Relative odds ratios for lack of clinical clearance between intervention categories (SCCIS lesions)

Heat/cold (C)	0.69 (0.13, 3.6)	0.29 (0.04, 2.17)	0.02 (<0.005, 0.15)
1.45 (0.28, 7.52)	PDT (E)	0.42 (0.07, 2.65)	0.02 (<0.005, 0.19)
3.42 (0.46, 25.34)	2.37 (0.38, 14.83)	Drugs (F)	0.06 (0.01, 0.58)
60.64 (6.87, 535.12)	41.96 (5.22, 337.2)	17.73 (1.72, 182.98)	No/sham treatment (I,J)

PDT=photodynamic therapy

Table 54 offers complementary information from the same analysis. The fraction of lesions without clinical clearance was between 10.8 and 29.2 percent in the active treatments and 88 percent with placebo. The confidence intervals for each estimate are wide.

Table 54. Mean and forecasted lack of clinical clearance fractions by intervention category (SCCIS lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
Heat/cold (C)	10.8 (3.1, 31.3)	10.8 (1.2, 54.7)
PDT (E)	14.9 (5.4, 34.9)	14.9 (1.9, 61.0)
Drug (F)	29.2 (8.4, 65.1)	29.2 (3.6, 82.2)
No/sham treatment (I,J)	88.0 (54.2, 97.8)	88.0 (34.7, 99.0)

PDT=photodynamic therapy

Comparisons across individual interventions

As is evident from Figure 18, there are two connected subgraphs: a smaller one comprising the comparison between cryotherapy (C1), MAL with ALA (E2) and 5-FU (F1), and a larger one between PDT with MAL with and without laser preparation (E1 and C5+E1), cryotherapy with 5-FU (C1+F1), and placebo. In total, five RCTs (436 lesions) were included in these analyses, as summarized in the box:

	First subgraph[68, 75, 79]	Second subgraph[76, 85]
Studies (total sample)	3 (330)	2 (106)
Total sample by intervention	(C5+E1): 32; (E1): 137; (C1+F1): 114; (J): 35; (F2): 12	(C1): 20; (E2): 53; (F1): 33
Total sample by intervention, (min, max)	12, 137	20, 53
Data by comparison	(C5+E1--E1): 1 (58); (E1--C1+F1): 1 (225); (E1--J): 1 (130); (C1+F1--J): 1 (133); (J--F2): 1 (28)	(C1--E2): 1 (40); (E2--F1): 1 (66)
Studies by comparison (min, max)	1, 1	1, 1
Total sample by comparison (min, max)	28, 225	40, 66
Followup median (min, max)	7 (3, 12) months	2.5 (2, 3) months

A: surgical excision, B: Mohs Micrographic Surgery; C1: cryotherapy; C3: diathermy and curettage; C4: cryotherapy and curettage; C5: laser; D1: external radiation; E1: MAL photodynamic therapy; E2: ALA photodynamic therapy; F1: 5-FU; F2: Imiquimod; F3: Interferon; F4: Ingenol; H: curettage; J placebo.

Table 55 shows the relative effects for both subgraphs, respectively. Because the comparisons across individual observations are sparse, however, the confidence intervals of the odds ratios for most indirect comparisons are broad and cannot exclude very large differences between the compared interventions.

Table 56 shows, for each intervention, the mean recurrence rates across all RCTs; estimates for interventions in both subgraphs are listed in the Table. One cannot compare statistically the estimated recurrence rates between an intervention in the first subgraph (e.g., PDT with MAL [E1]) and the second subgraph (e.g., cryotherapy [C1]), because they come from disjoint analyses.

Table 55. Relative odds ratios for lack of clinical clearance between individual interventions (SCCIS lesions).

Cryotherapy + 5-FU (C1+F1)	13.7 (2.92, 64.25)	2.11 (0.88, 5.06)	3.04 (0.21, 44.58)	0.04 (0.01, 0.15)			
0.07 (0.02, 0.34)	Laser + PDT (MAL) (C5+E1)	0.15 (0.04, 0.56)	0.22 (0.01, 4.18)	<0.005 (<0.005, 0.02)			
0.47 (0.2, 1.14)	6.49 (1.79, 23.58)	PDT (MAL) (E1)	1.44 (0.1, 21.22)	0.02 (0.01, 0.07)			
0.33 (0.02, 4.81)	4.5 (0.24, 84.77)	0.69 (0.05, 10.21)	Imiquimod (F2)	0.01 (<0.005, 0.19)			
22.62 (6.89, 74.26)	310.05 (51.68, 1860.02)	47.78 (13.39, 170.52)	68.87 (5.18, 915.22)	Placebo/sham (J)			
					Cryotherapy (C1)	0.28 (0.01, 7.38)	0.06 (<0.005, 1.59)
					3.59 (0.14, 95.23)	PDT (ALA) (E2)	0.21 (0.04, 1.08)
					16.9 (0.63, 453.4)	4.7 (0.93, 23.88)	5-FU (F1)

PDT=photodynamic therapy

Table 56. Mean and forecasted lack of clinical clearance fractions by intervention category (SCCIS lesions).

Intervention type	Mean percent (95% CI)	Forecast percent (95% CI)
First subgraph		
Cryotherapy + 5-FU (C1+F1)	41.3 (9.4, 82.7)	41.3 (2.3, 95.5)
Laser + PDT (MAL) (C5+E1)	4.9 (0.6, 31.0)	4.9 (0.1, 64.4)
PDT (MAL) (E1)	25.0 (4.9, 68.5)	25.0 (1.1, 90.8)
Imiquimod (F2)	18.8 (1.7, 75.5)	18.8 (0.5, 91.4)
Placebo (J)	94.1 (67.9, 99.2)	94.1 (33.1, 99.8)
Second subgraph		
Cryotherapy (C1)	2.6 (0.1, 35.5)	2.6 (0.1, 40.3)
PDT (ALA) (E2)	8.8 (2.4, 27.6)	8.8 (1.6, 36.4)
5-FU (F1)	31.2 (10.7, 63.2)	31.2 (7.3, 72.3)

PDT=photodynamic therapy

Lack of clinical clearance, other subgroup analyses (lesion location, lesion size), SCC lesions

Evidence from RCTS

Table 57 below shows results on subgroup analyses for a four-arm RCT.[73, 75] Neither lesion location nor size were associated with differences in the treatment effect beyond what is expected by chance.

Table 57. Subgroup analyses by lesion location and size: results for lack of clinical clearance (SCCIS lesions)

Study	Comparison	Time point	Subgroup	n/N arm 1 vs. n/N arm 2 vs. n/N arm 3	OR (95% CI); P-Value Within	P- Value Between
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	after first treatment	lesion diameter: 5-14 mm	4/30 vs. 5/42 vs. 6/7	1.14 (0.28, 4.65); 0.03 (0.00, 0.27); 0.02 (0.00, 0.23); p<0.001	p=0.457
			lesion diameter: 15-29 mm	21/65 vs. 11/48 vs. 7/10	1.61 (0.69, 3.76); 0.20 (0.05, 0.87); 0.13 (0.03, 0.58); p=0.016	
			lesion diameter: >= 30 mm	10/18 vs. 7/21 vs. 2/2	2.50 (0.68, 9.16); 0.25 (0.01, 5.87); 0.10 (0.00, 2.44); p=0.102	
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	after last treatment	lesion diameter: 5-14 mm	3/30 vs. 2/42 vs. 6/7	2.22 (0.35, 14.20); 0.02 (0.00, 0.21); 0.01 (0.00, 0.11); p<0.001	p=0.522
			lesion diameter: 15-29 mm	10/65 vs. 5/48 vs. 7/10	1.56 (0.50, 4.91); 0.08 (0.02, 0.35); 0.05 (0.01, 0.26); p<0.001	
			lesion diameter: >= 30 mm	4/18 vs. 1/21 vs. 2/2	5.71 (0.58, 56.73); 0.06 (0.00, 1.55); 0.01 (0.00, 0.47); p=0.007	
Morton 2006 16785375	Cryotherapy (C1) or 5-FU (F1) vs. MAL-PDT (E1) vs. sham PDT (J)	after last treatment	lesion location: extremities	12/72 vs. 6/69 vs. 11/12	2.10 (0.74, 5.95); 0.02 (0.00, 0.15); 0.01 (0.00, 0.08); p<0.001	NA
			lesion location: face/scalp	5/27 vs. 1/28 vs. 3/5	1.56 (0.50, 56.48); 0.15 (0.02, 1.16); 0.02 (0.00, 0.36); p=0.007	
			lesion location: neck/trunk	0/15 vs. 1/14 vs. 1/2	0.29 (0.01, 7.74); 0.03 (0.00, 1.20); 0.08 (0.00, 2.39); p=0.062	

NA = not significant; PDT = photodynamic therapy

Evidence from NRCSs

One NRCS reported lack of clinical clearance for 80 SCCIS lesions in 67 people, treated with either curettage (44 lesions) or cryotherapy (36 lesions). This study was deemed to be of high risk of bias, primarily for lack of reporting (baseline data and dropout numbers were not given by

arm), but also for lack of blinding. The mean age was 74 (range: 46 to 89), and the mean lesion area was 336 mm^2 (range 30 to 1890 mm^2). Eighty-two percent were female, and the lesions were located on the extremities (84%), trunk (7.5%), and head/neck (8.5%). The cryotherapy arm had a higher rate of lack of clinical clearance at 2 weeks (2 of 36 vs. 0 of 44).[137]

Patient-reported cosmetic outcomes, all SCC lesions

We did not identify any studies with results for this outcome in this population.

Observer-reported cosmetic outcomes, all SCC lesions

In this section, we describe only the results between intervention categories, because data are sparse for the comparison of individual observations. In total, two RCTs (204 lesions) were included in this analysis, both at low to moderate risk of bias for this outcome.[68, 75]The evidence graph in Figure 19 shows the observed comparisons based on RCTs that report observers' (investigators' or providers') assessments of "at least good" cosmetic outcome. The cosmetic outcome was assessed using different scales in each RCT. The evidence graph is sparsely connected. Details about the comparisons are in the box:

Studies (total sample)	2 (204)
Total sample by intervention	(C5+E1): 18; (E1): 100; (C1+F1): 86
Total sample by intervention, (min, max)	18, 100
Data by comparison	(C5+E1--E1): 1 (36); (E1--C1+F1): 1 (168)
Studies by comparison (min, max)	1, 1
Total sample by comparison (min, max)	36, 168
Followup (min, max)	12, 12 months

C1: cryotherapy; C3: diathermy and curettage; C4: cryotherapy and curettage; C5: laser; D1: external radiation; E1: MAL photodynamic therapy; E2: ALA photodynamic therapy; F1: 5-FU; F2: Imiquimod; F3: Interferon; F4: Ingenol; H: curettage; J placebo.

Figure 19. Evidence graph of RCTs comparing observer-assessed cosmetic outcomes (all SCC lesions)

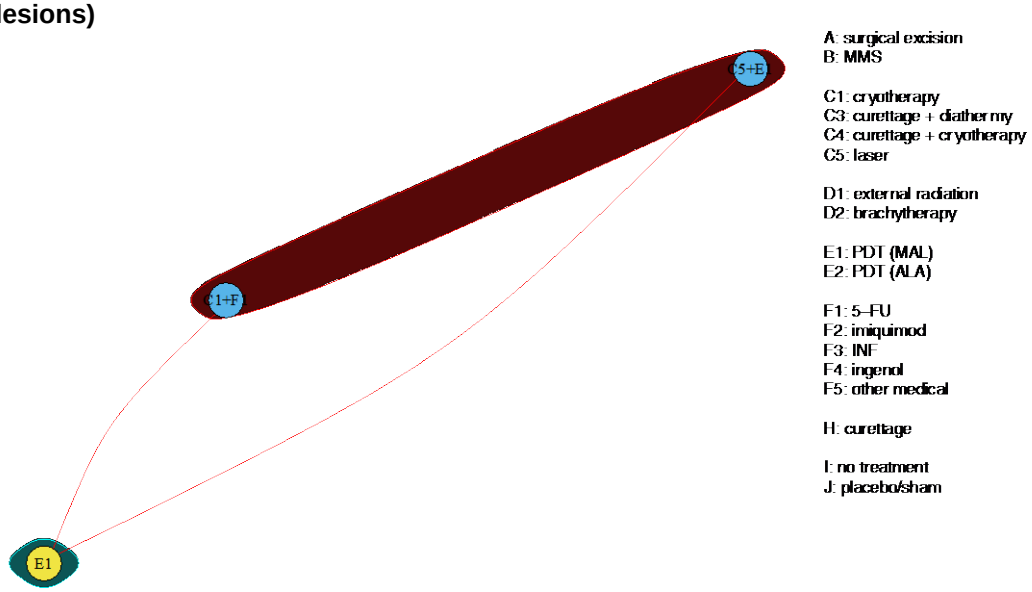


Table 58 has the results of the comparisons between intervention categories based on a network meta-analysis. Based on the odds ratios in the Table, the combination of cryotherapy and 5-FU (C1+F1) had statistically significantly better observer-assessed cosmetic outcomes than PDT with MAL (E1). The other two comparisons were not statistically significant. However, based on their confidence intervals one could not exclude differences in the odds of the outcome as large as 50 percent in either direction.

Table 58. Relative odds ratios between interventions for at least good cosmetic outcome, as assessed by an observer (SCCIS lesions)

Cryotherapy+5-FU (C1+F1)	0.32 (0.07, 1.51)	0.09 (0.02, 0.30)
3.1 (0.66, 14.5)	Laser + PDT (MAL) (C5+E1)	0.26 (0.04, 1.71)
11.71 (3.37, 40.66)	3.78 (0.58, 24.48)	PDT (MAL) (E1)

PDT = photodynamic therapy

Table 59 shows the average percentage of patients with at least good cosmetic outcomes in the RCTs, based on the same network meta-analysis as the Table above. The average number of lesions with cosmetic outcomes rated as good or excellent ranged between 72.1 and 96.8; however, the confidence intervals for these proportions were wide. Refer to the previous Table for a pairwise comparison between these treatments.

Table 59. Mean fractions of lesions with at least good cosmetic outcome, as assessed by an observer (SCCIS lesions)

Intervention	Mean percent (95% CI)
Cryotherapy + 5-FU (C1+F1)	72.1 (61.7, 80.5)
Laser + PDT (MAL) (C5+E1)	88.9 (64.8, 97.2)
PDT (MAL) (E1)	96.8 (90.5, 99.0)

PDT = photodynamic therapy

Evidence from NRCSs

No NRCS reported the outcome of interest in populations where the majority of lesions were SCCs. Refer to the section on this outcome in the BCC section for a description of an NRCS that included SCCs (29%) and compared a lower dose of radiation (37 Gy) with a higher dose (45 Gy). For observer assessed cosmetic outcomes and among all lesions, the relative risk favored the lower dose, but not statistically significantly so.[147]

Quality of life, SCC lesions

We did not identify any studies with results for this outcome in this population.

Mental health, SCC lesions

We did not identify any studies with results for this outcome in this population.

Patient satisfaction, SCC lesions

We did not identify any studies with results for this outcome in this population.

Mortality, SCC lesions

We did not identify any studies with results for this outcome in this population.

Costs and resource use, SCC lesions

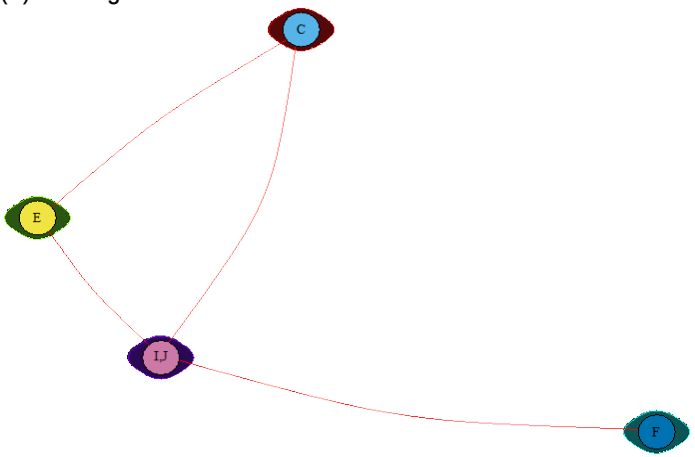
We did not identify any studies with results for this outcome in this population.

Adverse events, all SCCIS lesions

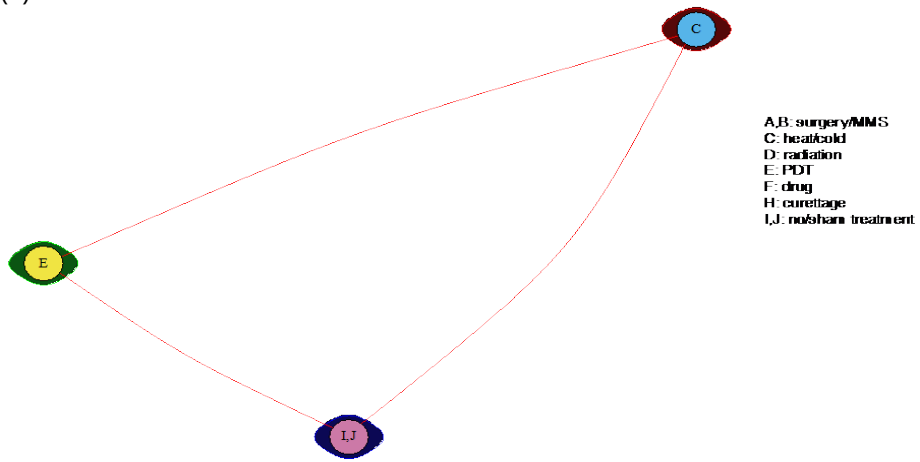
We describe only results between intervention categories, because data are sparse for the comparison of individual observations. Figure 20 shows the evidence graph for the comparison of the frequency of adverse events leading to discontinuation, serious adverse events, pain after treatment completion, and infection of the treated site. Reporting of adverse events was not consistent across RCTs. The Appendix enumerates other types of adverse events that were reported.

Figure 20. Evidence graph of RCTs comparing frequency of adverse events (SCCIS lesions)

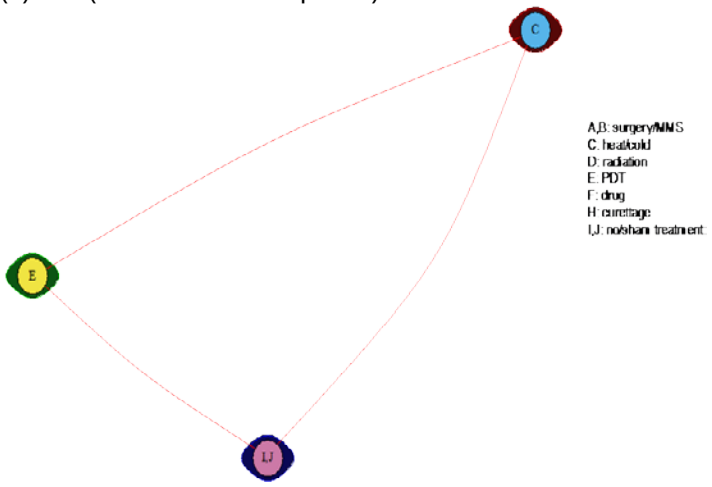
(A) Leading to treatment discontinuation



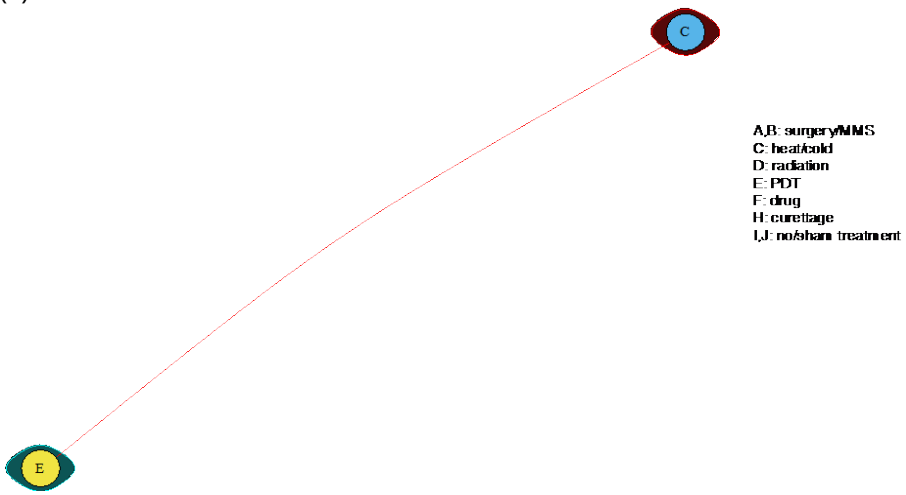
(B) Serious adverse events



(C) Pain (after treatment completion)



(D) Infection of the treated site



The evidence graphs in Figure 20 are sparsely connected. For parsimony, we do not report relative effects for comparisons of the frequency of each type of adverse event. The box has details about the comparisons by type of adverse event.

	Adverse events leading to treatment discontinuation[68, 75, 79]	Serious adverse events[75]	Pain after treatment[75, 76]	Infection of treated site[68]
Studies (total sample)	3 (292)	1 (225)	2 (265)	1 (36)
Total sample by intervention	(C): 130; (E): 114; (I,J): 33; (F): 15	(C): 112; (E): 96; (I,J): 17	(C): 132; (E): 116; (I,J): 17	(C): 18; (E): 18
Total sample by intervention, (min, max)	15, 130	17, 112	17, 132	18, 18
Data by comparison	(C--E): 2 (244); (C--I,J): 1 (129); (E--I,J): 1 (113); (I,J--F): 1 (31)	(C--E): 1 (208); (C--I,J): 1 (129); (E--I,J): 1 (113)	(C--E): 2 (248); (C--I,J): 1 (129); (E--I,J): 1 (113)	(C--E): 1 (36)
Studies by comparison (min, max)	1, 2	1, 1	1, 2	1, 1
Total sample by comparison (min, max)	31, 244	113, 208	113, 248	36, 36
Followup median (min, max)	[during treatment]	3 (3, 3) months	1.5 (0.3, 3) months	1 week

A: surgical excision, B: Mohs Micrographic Surgery; C: heat/cold; D: radiation; E: photodynamic therapy; F: drugs; H: curettage; I: no treatment; J: placebo.

We report rates of adverse events per intervention category, based on a joint analysis of all RCTs reporting the same outcome. Most likely, adverse events were defined differently across studies, but these definitions were often not clearly described. Results for different types of adverse events, as defined by each study, are in Table 60 and come from different analyses.

Drugs had the highest rate of adverse events leading to treatment discontinuation was (13.3%; 95% CI, 3.4 to 40.5); the rate for interventions destroying the lesion with heat or cold was 2.0 percent (C). This outcome was not applicable for PDT, because it is a one-time intervention.

The frequency of adverse events characterized as "serious" by the investigators was smaller than 1 percent for all intervention categories.

Rates of pain after treatment ranged between 23.4 and 34.1 percent (including sham treatments).

The outcome of infection at the treatment site was reported in a single RCT at 0 percent.[68]

Table 60. Mean fractions of adverse events, using each RCT's definitions (SCCIS lesions)

Intervention type	(A) Leading to discontinuation		(B) Serious*	(C) Pain after treatment		(D) Infection of the treated site*
	Mean	Forecast	Mean	Mean	Forecast	Mean
Heat/cold (C)	1.9 (0.6, 6.4)	1.9 (0.6, 6.4)	0.9 (0.1, 6.1)	34.1 (20.0, 51.6)	34.1 (14.7, 60.9)	0 (0, 31)
PDT (E)	Not defined**	Not defined**	0.5 (0.0, 7.7)	23.4 (12.4, 39.5)	23.4 (9.0, 48.5)	0 (0, 31)

Drugs (F)	13.3 (3.4, 40.5)	13.3 (3.4, 40.5)	NA	NA	NA	NA
No/sham treatment (I,J)	4.7 (0.9, 20.1)	4.7 (0.9, 20.1)	0 (0, 32.2)	28.4 (9.7, 59.3)	28.4 (7.8, 65.0)	NA

* No forecasts for these outcomes (fixed effects analyses only); ** PDT is a one-time treatment; discontinuation is not defined, but for parsimony, it was entered as 0 in the analysis; NA: not applicable.

Evidence from NRCSs

One NRCS reported pain for 80 SCCIS lesions in 67 people, treated with either curettage (44 lesions) or cryotherapy (36 lesions). The mean age was 74 (range: 46 to 89), and the mean lesion area was 336 mm2 (range 30 to 1890 mm2). Eighty-two percent were female, and the lesions were located on the extremities (84%), trunk (7.5%), and head/neck (8.5%). The cryotherapy arm had a significantly higher patient-reported pain during the treatment to 1 day after the procedure (OR 10.4; P-value <0.001).[137]

Invasive SCC lesions

We found no comparative studies on treatments of interest for invasive SCCs.

Discussion

Evidence Summary

Tables 61 and 62 summarize our conclusions on comparisons between types of intervention for treating BCCs and SCCIS, respectively.

The conclusions in the Tables are general and do not cover all the analyses we explored. We estimated effects for 213 comparisons between intervention categories and 565 comparisons between individual interventions for the outcomes of interest, not counting information from dose-response analyses (e.g., Table 44) and from nonrandomized studies. Providing conclusions and rating the "strength of the evidence" for each of these hundreds of comparisons is not productive. Consumers of our report who have specific interests should consult the pertinent results.

Within the existing evidence, with respect to BCC recurrence, surgical treatments and radiation therapy appear to be (statistically significantly) better than interventions that destroy lesions with heat or cold, PDT, or curettage. However, PDT was associated with improved cosmetic outcomes. With regards to drugs for the treatment of BCC, interferon was the only drug for which a randomized comparison for recurrence was identified. While it was associated with low recurrence rates, the confidence intervals were wide and so we cannot rule out excellent or poor results for that intervention category (Table 7).

Given that lack of recurrence is, essentially, cure from disease, these results support the use of surgical and radiation treatment for low-risk BCC. For SCCIS, the use of cryotherapy and PDT is supported over topical 5-fluorouracil with regards to recurrence. However, how these treatments perform for SCCIS compared with surgical treatments, which are commonly used in clinical practice, is not ascertainable based on the currently available evidence.

For patients and clinicians, though, cure is not the only important endpoint. Surgery, radiation and each of the other treatments under study are associated with benefits and drawbacks that patients and clinicians consider routinely. For example, while external beam radiation therapy is effective, its remote sequelae, such as skin atrophy and the development of secondary tumors, make it less advisable for younger patients. For patients for whom cosmesis is a primary concern, treatment with PDT may be preferable despite its higher recurrence rates. Despite sparse evidence on their ability to cure BCC and SCCIS, some patients may prefer the convenience provided by topical medical treatments such as 5-fluorouracil and imiquimod which can be applied by the patient at home; this contrasts with the multiple visits to hospitals or specialty clinics required for radiation therapy which are not be practical for some patients. Access to treatments will also impact clinical decisionmaking; specialty care is not available in all communities; while primary care physicians can perform basic surgical procedures and prescribe topical medications, they do not have access to specialized treatments such as MMS, radiotherapy and PDT.

Perhaps the most striking observation is the dearth of information that is available comparing interventions for these very common cancers. For example, consider comparisons between interventions for BCC lesion recurrence (Figure 7), a most important outcome from a clinical, public health and cost perspective.

Within the existing evidence, with respect to BCC recurrence, surgical treatments and radiation therapy appear to be (statistically significantly) better than interventions that destroy lesions with heat or cold, PDT, or curettage. Comparisons of either surgery or radiation therapy

versus interferon (the only drug for which a randomized comparison for recurrence was identified) were non-informative (the confidence intervals were very wide and encompassed double-digit odds ratios; Table 7). Only 11 RCTs (n=1234 lesions) examining BCC recurrence were included, of which only 15 lesions were treated with a drug (interferon) and only 20 were treated with curettage. Further, the amount of evidence in the 8 comparisons with head to head data was limited: the number of RCTs per comparison ranged between 1 and 3, and the cumulative number of lesions ranged between 27 and 347.

For SCCs, data on recurrence are even sparser. First, no study examined invasive SCCs, the subgroup of lesions that are most likely to recur or metastasize, and thus most important to evaluate. In clinical practice, these lesions are routinely treated with surgical excision with or without intraoperative margin evaluation, and in most cases are considered appropriate for Mohs surgery in the American Academy of Dermatology appropriate use criteria.[154] Radiation is also commonly used for invasive SCC. The lack of evidence comparing efficacy among these commonly used treatments is striking.

For SCCISs, only 4 RCTs (348 lesions) compared 4 types of interventions, namely a drug (imiquimod), interventions that destroy lesions with heat or cold, PDT, and sham treatments (Figure 16 [B] and Table 46). Note that surgical interventions, radiation therapy and curettage, therapies commonly used in clinical practice, were not examined.

Table 61. Summary conclusions for BCC lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, all BCC						
(1) Surgical interventions (A,B) and radiation (D) were associated with lower recurrence rates than interventions that destroy lesions with heat or cold (C), and PDT (E) (moderate to high strength of evidence) (2) Curettage (H) may have higher recurrence rates than surgical interventions (A,B) or radiation (D) (3) [Imprecise data on the comparison on curettage and interventions that destroy lesions with heat or cold (C) or PDT (E)] (4) [Imprecise data on the relative effects of interferon (F) versus other intervention categories]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 7 and 8)	Mix of direct and indirect data	(1) Moderate to High (2) Low (3) [Insufficient] (4) [Insufficient]	• Surgery/MMS (A,B) had significantly fewer recurrences than heat/cold, PDT, and curettage; not significantly fewer than radiation; and not significantly more than drugs (7 RCTs; 2 NRCSs) • Heat/cold (C) interventions had significantly more recurrences than surgery and radiation; not significantly more than drugs and curettage, and not significantly fewer than PDT (7 RCTs) • Radiation (D) had significantly fewer recurrences than thermal interventions and PDT, not significantly fewer than curettage, and not significantly more than surgery and drugs (3 RCTs) • PDT (E) had significantly more recurrences than radiation and surgery, and not significantly more than heat/cold, drugs, and curettage (6 RCTs, 1 NRCS) • Interferon (F) had fewer recurrences than all other interventions, but not significantly in any case (1 RCT, 1 NRCS) • Curettage (H) had significantly more recurrences than surgery, not significantly more recurrences than drugs and radiation, and not significantly fewer recurrences than PDT and heat/cold (2 RCTs)
Histologic clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better histological clearance outcomes and were statistically significantly better than interventions that destroy lesions with heat or cold (C), PDT (E), drugs (F), and placebo (I,J). (2) Interventions that destroy lesions with heat or cold (C), PDT (E), and drugs (F) have better histological outcomes than placebo (I,J) (3) [imprecise data on the relative comparisons of non-surgical active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 17 and 18)	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed significantly better than heat/cold, drugs, and placebo, and non-significantly better than PDT (2 RCTs) • Thermal interventions (C) performed significantly better than placebo, non-significantly better than drugs, non-significantly worse than PDT, and significantly worse than surgery (2 RCTs) • PDT (E) performed significantly better than placebo, non-significantly better than drugs and heat/cold, and non-significantly worse than surgery (7 RCTs, 1 NRCS) • Drugs (F) performed significantly better than placebo, non-significantly worse than PDT and heat/cold, and significantly worse than surgery (8 RCTs, 2 (NRCSs)
Clinical clearance, all BCC						
(1) Surgical interventions (A,B) were associated with better clinical clearance outcomes than PDT (E), drugs (F) and placebo (I,J) (2) All active treatments were associated with better clinical clearance outcomes than placebo (3) [Imprecise data on relative comparisons between non-surgical active treatments]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 28 and 29)	Mix of direct and indirect data	(1) High (2) Moderate to high (3) [Insufficient]	• Surgery (A,B) performed statistically significantly better than drugs and placebo, and non-significantly better than heat/cold and PDT (4 RCTs); this comparison is less relevant as surgery ought to achieve 100% clinical clearance • Thermal interventions (C)performed statistically significantly better than plecebo, non-significantly better than drugs and PDT, and non-significantly worse than surgery (3 RCTs) • PDT (E) performed statistically significantly better than placebo, non-significantly better than drugs, and non-significantly worse than surgery and heat/cold (7 RCTs)

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
						• Drugs (F) performed statistically significantly better than placebo, non-significantly worse than PDT and heat/cold, and significantly worse than surgery (5 RCTs)
Patient-reported cosmetic outcomes, all BCC						
(1) PDT is associated with better cosmetic outcomes than other intervention categories (2) [Imprecise data on relative comparisons between non-surgical active intervention categories]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons (Refer to Tables 38, 39)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Low (2) Insufficient	• Surgery(A,B) had significantly better outcomes than heat/cold and radiation, significantly worse outcomes than PDT, and non-significantly worse outcomes than drugs (4 RCTs) • Thermal interventions (C)had significantly worse outcomes than surgery and PDT and non-significantly worse than radiation and drugs (2 RCTs) • Radiation (D) had non-significantly better outcomes than heat/cold, non-significantly worse outcomes than drugs, and significantly worse outcomes than PDT and surgery (2 RCTs) • PDT (E) had significantly better outcomes than surgery, heat/cold, and radiation and non-significantly better outcomes than drugs (4 RCTs) • Drugs (F) had better outcomes than surgery, heat/cold, and radiation, and non-significantly worse outcomes than PDT, but not statistically significantly so (1 RCT)
Observer-reported cosmetic outcomes, all BCC						
(1) PDT is associated with significantly better cosmetic outcomes than surgery (A,B) (2) [PDT may be associated with better cosmetic outcomes compared to nonsurgical active intervention categories] (3) [Imprecise data on relative comparisons between heat/cold (C), radiation, and drugs (D)]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. Imprecise for most comparisons (Refer to Tables 40, 41)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) [Insufficient] (3) [Insufficient]	• Surgery(A,B) had non-significantly better outcomes than radiation, significantly worse outcomes than PDT, and non-significantly worse outcomes than drugs, heat/cold, and placebo (4 RCTs, 1 NRCS) • Heat/cold interventions (C) had significantly better outcomes than radiation, non-significantly better outcomes than surgery, and non-significantly worse outcomes than PDT, drugs, and placebo (1 RCT) • Radiation (D) had significantly worse outcomes than heat/cold, PDT, drugs, and placebo, and non-significantly worse outcomes than surgery (1 RCT, 2 NRCS) • PDT (E) had significantly better outcomes than surgery and radiation, non-significantly better outcomes than drugs and heat/cold, and non-significantly worse outcomes than placebo (7 RCTs, 1 NRCS) • Drugs (F) had significantly better outcomes than radiation, non-significantly better outcomes than surgery and heat/cold, and non-significantly worse outcomes than PDT and placebo (1 RCT)
Adverse effects, all BCC						

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
(1) Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with surgical interventions (A,B), heat or cold (C), PDT (E) and drugs (F) (2) For the interventions above, on average, 1 in 10 to 1 in 5 patients report experiencing pain after treatment	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events have wide 95% CIs (Table 43)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) Moderate (2) Low	• For active interventions, point estimates for percentage of discontinuation of treatment, serious adverse events, and infection of the treatment site range from 0/not defined to 5.5%. Forecast CIs are wide (as high as 29%; Table 43) • For active interventions, point estimates for the percentage of pain after treatment range between 9.9 and 21.6%. Forecast CIs are wide (as high as 88%; Table 43)
Other outcomes, all BCC						
[Evidence on quality of life, mental health, patient satisfaction, mortality, cost and resource use is reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

Table 62. Summary conclusions for SCCIS lesions and strength of the relevant evidence

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Recurrence, SCCIS						
(1) Interventions that destroy the lesions with heat or cold (C) and PDT (E) were associated with lower recurrence rates than 5 FU (F) (2) [Imprecise data on the relative effect of thermal interventions versus PDT]	Moderate	Possibly consistent (No robust indications of inconsistency)	Moderately precise. Varies by comparison from precise to imprecise. (Refer to Tables 46 and 47)	Mix of direct and indirect data	(1) Low (2) [Insufficient]	• Thermal interventions (C) had statistically significantly fewer recurrences than drugs, and not significantly fewer than PDT or placebo (2 RCTs) • PDT (E) had statistically significantly fewer recurrences than drugs, but not statistically significantly fewer than placebo or more than heat/cold (4 RCTs) • Drugs (F) had statistically significantly more recurrences than heat/cold and PDT, and not significantly more than placebo (1 RCT)
Histologic clearance, SCCIS						
(1) [Laser (C5) + PDT with ALA (E2) results in better histologic clearance over laser alone] (2) 5-FU (F) results in better histologic clearance than placebo (I,J)	(1) Low (2) High	[Not rated]	(1) Imprecise (2) Precise	(1) Direct (2) Direct	(1) [Insufficient] (2) Low	[2 RCTs, 50 patients. See Tables 51, 52]
Clinical clearance, all SCCIS						
(1) Examined types of active interventions (heat/cold [C], PDT (E), and drugs [5-FU, imiquimod; F]) were associated with better clinical outcomes than placebo (2) [Imprecise data on relative comparisons between types of active interventions]	Moderate	Possibly consistent (No robust indications of inconsistency)	Varies by comparison from precise to imprecise. (Refer to Tables 53 and 54)	Mix of direct and indirect data	(1) High (2) [Insufficient]	• Thermal interventions (C) performed significantly better than placebo, and non-significantly better than drugs and PDT (4 RCTs) • PDT (E) performed significantly better than placebo, non-significantly better than drugs, and non-significantly worse than heat/cold (5 RCT) • Drugs (F) (5-FU, imiquimod) performed significantly better than placebo, and non-significantly worse than PDT and heat/cold (2 RCT)
Observer-reported cosmetic outcomes, SCCIS						
(1) Cryotherapy plus 5-FU (C1+F1) is associated with better outcomes than PDT (MAL) (E1) (2) [No difference between laser pre-treatment of the lesion before PDT versus PDT alone]	Low	Unclear (Consistency cannot be rated)	(1) Precise (2) Imprecise (Refer to Tables 58, 59)	Mix of direct and indirect data	(1) Moderate (2) [Insufficient]	[2 RCTs, 204 patients. See Tables 58, 59]
Adverse effects, SSCIS						
(1) [Serious adverse events, adverse events leading to discontinuation and infections of the treated site are uncommon with heat or cold (C), PDT (E) and drugs (F)] (2) [On average, 1 in 4 and 1 in 3 patients report experiencing pain after treatment with PDT (E) and heat or cold (C), respectively]	High (selective reporting bias)	Unclear (Consistency cannot be assessed)	Imprecise We do not report relative effects. Forecasted percentages of patients with adverse events have wide 95% CIs (Table 60)	Mix of direct and indirect data (most comparisons based on indirect data)	(1) [Insufficient] (2) [Insufficient]	[3 RCTs 292 patients. See Table 60]

Conclusion statement	RoB (evidence -base)	Consistency	Precision	Directness	Overall Rating	Comments
Other outcomes, SCCIS						
[Evidence on patient reported cosmetic outcomes, quality of life, mental health, patient satisfaction, mortality, cost and resource use id reported in a minority of studies and its strength not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]
Other analyses						
[Subgroup analyses and analyses focusing on individual interventions are generally sparse and are not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]	[Not rated]

Evidence Limitations

With few exceptions and for most outcomes, individual studies were deemed to have at most moderate risk of confounding, selection, or measurement biases. The risk of bias of individual studies was not a major determinant for the conclusions in Tables 60 and 61. Assessing impact of the risk of bias of individual studies on the conclusions of a network meta-analysis is not straightforward.[155] The comparison effects estimated from a network meta-analysis are a combination of the estimated effects from head-to-head studies and from studies contributing through indirect comparisons. For example, assume that there is a highly-biased study in a network meta-analysis: it would be a concern primarily for the comparison it directly informs on, it may be a smaller (or even negligible) concern for comparisons that it informs indirectly, and it will be no concern for comparisons to which it contributes zero information.[156] In this analysis we deemed qualitatively that risk of bias concerns would not change our conclusions. While qualitative-only assessments are precarious, we opted for high-level conclusions that may be robust.

By far the major concern, however, is that the evidence is sparse when one considers the richness of the clinical questions that can be posed. Comparisons between intervention categories are not as informative as comparisons between individual interventions. We have provided analyses at the individual intervention level, but opt not to draw conclusions based on them, because most are based on indirect data and small numbers.

Another consequence of the paucity of evidence base is that one cannot directly address questions that may have important health and cost implications for insurers and patients. For example, there are no studies on the effectiveness of external radiation therapy delivered with portable machines in the office setting versus radiation therapy delivered in specialized facilities or versus other interventions. Empirical data on this radiation therapy modality would be useful because there are only limited data on radiation therapy to extrapolate from.

Other large gaps remain in the knowledge base: There is no information on subgroups of patients who have limited life expectancy, are frail, or who are immunocompromised (e.g., have CLL and other malignancies, immunodeficiency disorders, or who receive immunomodulating or immunosuppressive treatments). There is limited or no information on high risk BCC lesions, and on invasive SCCs. There is limited data on patient- and lesion-specific modifiers of intervention effects.

Finally, outcomes such as histological clearance and clinical clearance are surrogates for lesion recurrence. In particular, clinical clearance may be informative when comparing among PDT, medical, and radiation-based therapies, but is not an informative outcome for surgical interventions: any surgical treatment, regardless of margin control, removes all clinically visible tumor. Therefore, our conclusion in Table 61 that surgical interventions are better than all other interventions with respect to clinical clearance, while very likely to be true, is almost meaningless.

Future Research Recommendations

We have identified a number of important gaps in the medical literature on the topic of treating BCC and SCC. They are described briefly in the following paragraphs.

More trials are needed comparing commonly used treatment modalities such as simple excision, Mohs surgery, PDT and topical medical therapy. Further, in order to justify routine use of various forms of radiotherapy for these patients, more trials comparing radiotherapy with other modalities are needed. As it stands, the lack of evidence on radiotherapy has led the American Academy of Dermatology to discourage the use of superficial radiotherapy and electronic brachytherapy for keratinocyte carcinomas except in select patients.[157, 158] As these tumors are very common and generally have low morbidity and mortality, recruitment for such trials may not prove to be prohibitively difficult.

All trials for BCC and SCC should, where possible, use recurrent disease as a primary or secondary outcome as it is the most clinically important outcome. Trials should also attempt to incorporate measures of healthcare resource utilization, which were lacking in our review of the existing evidence save for one RCT and one NRCS[19, 151].

While more evidence is needed overall, future research should also focus on specific subgroups that have minimal evidence to date. Aggressive histologic subtypes of BCC, including infiltrative and sclerosing patterns, account for very little of the evidence found in our review. While their increased likelihood of recurrence has led to their inclusion as appropriate indications for Mohs surgery (except for lesions ≤0.5 cm on the trunk and extremities, whose appropriateness is rated as "uncertain"), there is scant evidence to support this.[154] With regards to SCC, the only RCT evidence included in this report concerns in situ disease. Given that invasive SCC is responsible for mortality in 3900-8800 people in the U.S. each year[5] in addition to morbidity and healthcare costs, there is a clear need for comparative effectiveness research for invasive SCC treatments. No comparative evidence was found on keratinocyte carcinoma in high-risk groups such as organ transplant recipients and patients with other altered immune states such as HIV and Chronic Lymphocytic Leukemia (CLL). Patients with limited life-expectancy are another subgroup of interest who warrant study.

Patients, clinicians, payers, and research funders would benefit from a decision analysis of the management of BCC and SCC lesions.

Finally, better monitoring of population trends in BCCs and SCCs can help focus research on most consequential subtypes. Such monitoring can be performed by SEER (which currently ignores these cancers), the CDC, or large health organizations taking advantage of advances in health information technology.

Conclusions

Based on sparse evidence, surgical, radiation and topical drug treatments have lower recurrence rates than other modalities for the treatment of low-risk BCC, and PDT appears to have superior cosmetic outcomes. Large gaps remain in the literature regarding the comparison of individual interventions, and very little or no information on immunocompromised patients, patients with limited life expectancy, and on patients with specific lesion categories, including high risk BCCs and invasive SCCs. In order for clinicians, patients and payers to make informed decisions regarding the treatment of these lesions, new RCT or high-quality NRCS evidence is needed.

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